

# Toxicology Research Laboratory

---

**UIC** The University of Illinois  
at Chicago

Department of Pharmacology (M/C 868)  
1940 W. Taylor St.  
Chicago, Illinois 60612-7353

**20100915238**

DRAFT

SECURITY CLASSIFICATION OF THIS PAGE

## REPORT DOCUMENTATION PAGE

Form Approved  
OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION			1b. RESTRICTIVE MARKINGS		
2a. SECURITY CLASSIFICATION AUTHORITY Unclassified			3. DISTRIBUTION / AVAILABILITY OF REPORT  Unlimited		
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE					
4. PERFORMING ORGANIZATION REPORT NUMBER(S)  UIC-10B (UIC/TRL Study No. 154)			5. MONITORING ORGANIZATION REPORT NUMBER(S)		
6a. NAME OF PERFORMING ORGANIZATION Toxicology Research Laboratory University of Illinois at Chicago		6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION  U.S. Army Medical Materiel Development Activity		
6c. ADDRESS (City, State, and ZIP Code) Department of Pharmacology (M/C 868) 1940 W. Taylor Street Chicago, IL 60612-7353			7b. ADDRESS (City, State, and ZIP Code) ATTN: MCMR-RMA-RD Fort Detrick Frederick, MD 21702-5014		
8a. NAME OF FUNDING / SPONSORING ORGANIZATION U.S. Army Medical Materiel Development Activity		8b. OFFICE SYMBOL (If applicable) MCMR-UMP	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER  DAMD17-92-C-2001		
8c. ADDRESS (City, State, and ZIP Code)  Fort Detrick Frederick, MD 21702-5009			10. SOURCE OF FUNDING NUMBERS		
			PROGRAM ELEMENT NO. 63807A	PROJECT NO. 30463807	TASK NO. QC
					WORK UNIT ACCESSION NO. 073
11. TITLE (Include Security Classification)  Developmental Toxicity (Segment II) Study of WR238605 Succinate in Rats					
12. PERSONAL AUTHOR(S) Levine, B.S., Youssef, A.F., and Mercieca, M. (PAI)					
13a. TYPE OF REPORT Study		13b. TIME COVERED FROM 06/28/94 TO		14. DATE OF REPORT (Year, Month, Day)	
				15. PAGE COUNT	
16. SUPPLEMENTARY NOTATION					
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)		
FIELD	GROUP	SUB-GROUP			
19. ABSTRACT (Continue on reverse if necessary and identify by block number)					
<p>This study evaluated the developmental toxicity of WR238605 Succinate in time-mated CD female rats. Doses were 0, 3, 10, and 30 mg base/kg/day administered by gavage during gestation days (GD) 6 - 15 (GD0 = day of vaginal plug). In addition, a positive control group was administered retinol palmitate, 1000 mg/kg/day, on GD9 and 10 by gavage. Maternal toxic manifestations were observed in the high dose and to a lesser extent in the mid dose and positive control groups. A significant decrease in body weight from GD8 resulting in a reduction in total weight gain was associated with a significant decrease in food consumption in high dose females (i.e., 30 mg base/kg/day). Mid dose females (i.e., 10 mg base/kg/day) showed significant decreases in body weight and food consumption only during the period of dosing (i.e., GD6 - 15). Other toxic manifestations were limited to rough coat in two animals at the high dose and enlarged spleen in 16 high dose and 1 mid dose animals. Toxicity was not observed in the low dose level. The positive control group showed a significant decrease in body weight and total weight gain from GD10 - GD20, in addition to a decrease in food consumption during the dosing period (i.e., GD6 - GD15).</p>					
20. DISTRIBUTION / AVAILABILITY OF ABSTRACT <input type="checkbox"/> UNCLASSIFIED/UNLIMITED <input checked="" type="checkbox"/> SAME AS RPT. <input type="checkbox"/> DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION Unclassified		
22a. NAME OF RESPONSIBLE INDIVIDUAL Barry S. Levine			22b. TELEPHONE (Include Area Code) (312) 996-5543		22c. OFFICE SYMBOL N/A



## SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
1a. REPORT SECURITY CLASSIFICATION			1b. RESTRICTIVE MARKINGS		
2a. SECURITY CLASSIFICATION AUTHORITY Unclassified			3. DISTRIBUTION / AVAILABILITY OF REPORT Unlimited		
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE					
4. PERFORMING ORGANIZATION REPORT NUMBER(S) UIC-10B (UIC/TRL Study No. 154)			5. MONITORING ORGANIZATION REPORT NUMBER(S)		
6a. NAME OF PERFORMING ORGANIZATION Toxicology Research Laboratory University of Illinois at Chicago		6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION U.S. Army Medical Materiel Development Activity		
6c. ADDRESS (City, State, and ZIP Code) Department of Pharmacology (M/C 868) 1940 W. Taylor Street Chicago, IL 60612-7353		7b. ADDRESS (City, State, and ZIP Code) ATIN: MCMR-RMA-RD Fort Detrick Frederick, MD 21702-5014			
8a. NAME OF FUNDING / SPONSORING ORGANIZATION U.S. Army Medical Materiel Development Activity		8b. OFFICE SYMBOL (If applicable) MCMR-UMP	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER DAMD17-92-C-2001		
8c. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, MD 21702-5009		10. SOURCE OF FUNDING NUMBERS	PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.
			63807A	30463807	QC
					WORK UNIT ACCESSION NO. 073
11. TITLE (Include Security Classification) Developmental Toxicity (Segment II) Study of WR238605 Succinate in Rats					
12. PERSONAL AUTHOR(S) Levine, B.S., Youssef, A.F., and Mercieca, M. (PAI)					
13a. TYPE OF REPORT Study		13b. TIME COVERED FROM 06/28/94 TO		14. DATE OF REPORT (Year, Month, Day)	
				15. PAGE COUNT	
16. SUPPLEMENTARY NOTATION					
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)		
FIELD	GROUP	SUB-GROUP	Rats		
			WR238605 Succinate		
			Developmental Toxicity		
19. ABSTRACT (Continue on reverse if necessary and identify by block number)					
<p>This study evaluated the developmental toxicity of WR238605 Succinate in time-mated CD* female rats. Doses were 0, 3, 10, and 30 mg base/kg/day administered by gavage during gestation days (GD) 6 - 15 (GDO = day of vaginal plug). In addition, a positive control group was administered retinol palmitate, 1000 mg/kg/day, on GD9 and 10 by gavage. Maternal toxicity was observed in the high dose and to a lesser extent in the mid dose. At the high dose, significant decreases in body weight, total weight gain and food consumption were observed throughout the study with rough coat seen in two animals. In addition, enlarged spleen was observed at necropsy in 16 high dose and 1 mid dose females. In the mid dose, marginal decreases in body weight and food consumption were observed during the dosing period. Maternal toxicity was not observed in the low dose. Doses of WR238605 succinate used in the present study were not developmentally toxic. Retinol palmitate (1000 mg/kg/day on GD 9 &amp; 10) was developmentally and maternally toxic. Significant decreases in body weight, total weight gain and uterine weights were observed. In addition, significant increases in fetal malformations and decreases in fetal body weights and the number of viable fetuses were observed. In conclusion, WR238605 succinate was maternally toxic in rats at 10 mg base/kg/day, however developmental toxicity was not observed up to 30 mg base/kg/day, the highest dose level tested.</p>					
20. DISTRIBUTION / AVAILABILITY OF ABSTRACT <input type="checkbox"/> UNCLASSIFIED/UNLIMITED <input checked="" type="checkbox"/> SAME AS RPT. <input type="checkbox"/> DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION Unclassified		
22a. NAME OF RESPONSIBLE INDIVIDUAL Barry S. Levine			22b. TELEPHONE (Include Area Code) (312) 996-5543		22c. OFFICE SYMBOL N/A

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

Title Page

Study Report for Task Order No. UIC-10B

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

Sponsor: U.S. Army Medical Materiel  
Development Activity

Test Article: WR238605 Succinate

Contract No.: DAMD17-92-C-2001

D  
R  
A  
F  
T

Study Director

Barry S. Levine, D.Sc., D.A.B.T.

In-Life Phase Completed On

November 4, 1994

Performing Laboratory

TOXICOLOGY RESEARCH LABORATORY (TRL)  
University of Illinois at Chicago (UIC)  
Department of Pharmacology  
1940 W. Taylor St.  
Chicago, IL 60612-7353

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other documentation.

DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

STATEMENT OF COMPLIANCE

To the best of my knowledge, Study No. 154 entitled "Developmental Toxicity (Segment II) Study of WR238605 Succinate in Rats" was conducted in compliance with the Good Laboratory Practices regulations as published in 21 CFR 58, 40 CFR 160 and 40 CFR 792 in all material aspects.

The protocol for this study was approved by the UIC Animal Care Committee.

Signature

Study Director

\_\_\_\_\_  
Barry S. Levine, D.Sc., D.A.B.T.

\_\_\_\_\_  
Date



QUALITY ASSURANCE STATEMENT

STUDY TITLE: DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

STUDY NUMBER: 154

STUDY DIRECTOR: BARRY S. LEVINE

INITIATION DATE: 6/28/94

This study has been divided into a series of phases. Using a random sampling approach, Quality Assurance personnel monitors each of these phases over a series of studies. Procedures, equipment, documentation, etc., are examined in order to assure that the study is performed in accordance with the Good Laboratory Practice regulations of the Food and Drug Administration and the Environmental Protection Agency to assure that the study is conducted according to the protocol.

The following are the inspection dates, phases inspected, and report dates of QA inspections of the study.

INSPECT ON 6/29/94, TO STUDY DIR 6/29/94, TO MGMT 6/29/94  
PHASES: PROTOCOL REVIEW

INSPECT ON 10/20/94, TO STUDY DIR 10/20/94, TO MGMT 10/26/94  
PHASES: MORIBUNDITY/MORTALITY, ROOM ENVIRONMENT, FOOD  
CONSUMPTION, BODY WEIGHT, DOSING AND CLINICAL SIGNS

INSPECT ON 11/1/94, TO STUDY DIR 11/2/94, TO MGMT 11/3/94  
PHASES: EUTHANASIA, C-SECTIONING OBSERVATIONS AND FETAL  
OBSERVATIONS AND EXAMINATIONS

INSPECT ON 1/17/95, TO STUDY DIR 1/17/95, TO MGMT 1/17/95  
PHASES: RAW DATA AND DRAFT REPORT FROM THE ANALYTICAL LAB

INSPECT ON 2/9/95, TO STUDY DIR 2/10/95, TO MGMT 3/29/95  
PHASES: RAW DATA

INSPECT ON 3/29-30/95, TO STUDY DIR 3/30/95, TO MGMT 3/30/95  
PHASES: DRAFT REPORT

  
\_\_\_\_\_  
QUALITY ASSURANCE

  
\_\_\_\_\_  
DATE

DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

Signature Page

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

TRL Chemical No.: 0720614

Sponsor: U.S. Army Medical Materiel  
Development Activity  
Fort Detrick  
Frederick, MD 21702-5009

Test Article: WR238605 Succinate

Sponsor  
Representative: George J. Schieferstein, Ph.D.

Testing Facility: TOXICOLOGY RESEARCH LABORATORY (TRL)  
University of Illinois at Chicago (UIC)  
Department of Pharmacology (M/C 868)  
1940 W. Taylor St.  
Chicago, IL 60612-7353

\_\_\_\_\_  
Barry S. Levine, D.Sc., D.A.B.T.  
Study Director

\_\_\_\_\_  
Date

\_\_\_\_\_  
Ashraf F. Youssef, M.D., Ph.D.  
Reproductive Toxicologist

\_\_\_\_\_  
Date

In-life Phase Initiation: October 12, 1994

Dosing Initiation: October 18, 1994

In-Life Completion: November 4, 1994

DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

TABLE OF CONTENTS

TITLE PAGE .....	1
STATEMENT OF COMPLIANCE .....	2
QUALITY ASSURANCE STATEMENT .....	3
SIGNATURE PAGE .....	4
TABLE OF CONTENTS .....	5
1. SUMMARY .....	7
2. INTRODUCTION .....	7
3. MATERIALS AND METHODS .....	7
3.1 Test Article .....	7
3.2 Animals .....	8
3.3 Experimental Design .....	9
3.4 Statistical Analyses .....	10
4. RESULTS .....	11
4.1 Dosage Formulation Analysis .....	11
4.2 Mortality/Clinical Signs .....	11
4.3 Maternal Body Weights .....	11
4.4 Food Consumption .....	12
4.5 Cesarean-Section and Maternal Gross Observations .....	12
4.6 Fetal Observations .....	12
5. DISCUSSION .....	12
6. REFERENCES .....	13
7. PERSONNEL .....	13
8. ARCHIVES .....	13

TABLES

1	Summary of Toxic Responses .....	14
2	Dosage Formulation Analyses .....	15
3	Summary of Clinical Signs .....	16
4	Summary of Body Weights (Maternal) .....	17
5	Summary of Weight Gains (Maternal) .....	19
6	Summary of Daily Mean Food Consumption .....	21
7	Summary of Cesarean-Section Data and Fetal Evaluations .....	22



DRAFT

APPENDICES

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

1	Analytical Chemistry Report .....	1-1
2	Individual Maternal Clinical Signs .....	2-1
3	Individual Maternal Body Weight and Weight Gain Data .....	3-1
4	Individual Maternal Food Consumption Data .....	4-1
5	Teratology Report .....	5-1
6	Protocol and Amendments .....	6-1
7	Study Deviations .....	7-1

# DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

## 1. SUMMARY

This study evaluated the developmental toxicity of WR238605 Succinate in time-mated CD® female rats. Doses were 0, 3, 10, and 30 mg base/kg/day administered by gavage during gestation days (GD) 6 - 15 (GD0 = day of vaginal plug). In addition, a positive control group was administered retinol palmitate, 1000 mg/kg/day, on GD9 and 10 by gavage. The results are summarized in Table 1. Maternal toxic manifestations were observed in the high dose and to a lesser extent in the mid dose and positive control groups. A significant decrease in body weight from GD8 resulting in a reduction in total weight gain was associated with a significant decrease in food consumption in high dose females (i.e., 30 mg base/kg/day). Mid dose females (i.e., 10 mg base/kg/day) showed significant decreases in body weight and food consumption only during the period of dosing (i.e., GD6 - 15). Other toxic manifestations were limited to rough coat in two animals at the high dose and enlarged spleen in 16 high dose and 1 mid dose animals. Toxicity was not observed in the low dose level. The positive control group showed a significant decrease in body weight and total weight gain from GD10 - GD20, in addition to a decrease in food consumption during the dosing period (i.e., GD6 - GD15).

The doses of WR238605 succinate tested in this study did not result in any developmental toxicity. The 3 mg base/kg/day dose was considered the maternal no observable effect level (NOEL) while 30 mg base/kg/day, the highest dose tested, was considered the NOEL for fetal toxicity in rats. Significant developmental toxic manifestations were, however, seen in the positive control group. These manifestations included significant decreases in the number of viable fetuses, fetal body weights and maternal uterine weights. In addition, significant increases in % postimplantation loss, and increased incidences in fetal skeletal and visceral malformations, primarily related to structures of the head, vertebral column and ribs, were noted in retinol palmitate-treated animals.

## 2. INTRODUCTION

This study was conducted to evaluate the developmental toxicity of WR238605 Succinate in rats. The test article was administered by daily gavage to time-mated CD® females during gestation days 6 - 15. The fetuses were delivered by Cesarean section on gestation day 20. They were examined for external anomalies and then fixed in either Bouin's solution or alcohol for subsequent internal examination. All methods and procedures in this study were conducted in accordance with the Toxicology Research Laboratory, University of Illinois at Chicago and Pathology Associates, Inc. Quality Assurance Programs designed to conform with FDA Good Laboratory Practices Regulations. No unforeseen circumstances affected the integrity of the study. This study was initiated on the night of October 12, 1994 (initiation of mating). Dosing was initiated (stagger-started over four days) on October 18, 1994 (GD6) and the in-life portion was terminated on November 4, 1994 (GD20).

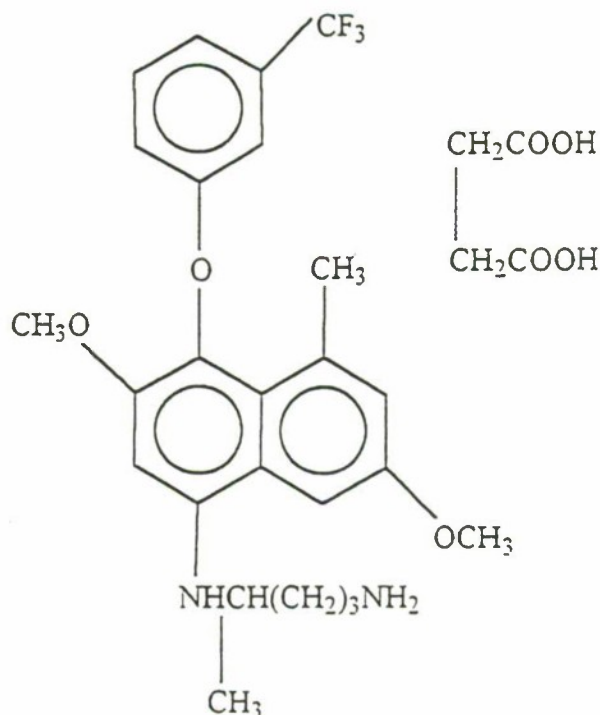
## 3. MATERIALS AND METHODS

### 3.1 Test Article

WR238605 Succinate (Bottle Lot No. BM 12562), a pale yellow powder, was received on 10/05/94 from Herner & Co., and was assigned an in-house chemical number (0720614). The chemical name of the test article is 8-[4-Amino-1-methylbutyl]amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethyl-phenoxy)quinoline succinate and the mole fraction of the base is 0.8. It was stored at 0 to 4°C and ambient humidity, and was protected from light (the container was wrapped in aluminum foil). The chemical structure follows.

# DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154



The test article was initially identified by GC-MS and the purity was determined to be 99.91%. The purity was re-determined following the completion of the in-life portion of the study. At that time, the purity was 99.94%. Thus, the test article was stable under storage conditions.

### 3.2 Animals

One hundred and fifty-six female Virus Antibody Free (VAF) time-mated CD® rats were obtained from Charles River Breeding Laboratories, Portage, MI on October 14 and 17, 1994. The animals were ≈ 9 weeks old upon arrival at the UIC AAALAC-accredited animal facility (date of birth 08/09/94 and 08/12/94). Each animal was given a study-unique number (ear-tag) by the supplier. This number appeared on a cage card visible on the front of each cage. The cage card additionally contained the study number, test article identification, treatment group number, and dose level. Cage cards were color-coded as a function of treatment group. Animals were singly housed in polycarbonate cages with Anderson Bed-a-cob bedding (Heinold Co., Kankakee, IL) in a temperature (65 - 78°F) and humidity (approx. 30 - 70 %) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 840 cm<sup>2</sup> area and 20 cm height, was adequate to house rats at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All animals were routinely transferred to clean cages with fresh bedding weekly.

Certified Rodent Chow No. 5002 (PMI Feeds, Inc., St. Louis, MO) and tap water from an automatic watering system in which the room distribution lines were flushed daily were provided *ad libitum* from arrival until termination. The water was not treated with additional chlorine or HCl. There were no known contaminants in the feed or water which were expected to influence the study. The results of the most current comprehensive chemical analyses of Chicago water conducted by the City of Chicago are documented in files maintained by Quality Assurance.



3.3 Experimental Design

The animals were mated on four sequential nights at the suppliers' facility. The morning when the vaginal plug was found was considered gestation day 0 (GD0). At each GD0, 39 females showing vaginal plugs were collected. Each animal was ear tagged and GD0 body weights were obtained by the supplier. Of the 156 presumed pregnant rats which were received, 39 were at GD1, 78 at GD2, and the other 39 were at GD3 upon arrival at the UIC animal facility. All animals were quarantined for at least 3 days before initiation of dosing on GD6. All animals were examined daily during the quarantine period, and were approved for use by the Clinical Veterinarian prior to being placed on test. Animals from each gestation day 0 subset were randomized into five groups on the basis of body weight to result in 25 animals/group. Dosing initiation and subsequent necropsies were staggered over 4 days.

Dose levels were selected on the basis of a range-finding developmental toxicity study in rats (UIC/TRL Study Nos. 153) as follows:

<u>Group No.</u>	<u>Treatment</u>	<u>Dose Level</u> (mg base/kg/day)	<u>Number of</u> <u>Females*</u>
1	Vehicle	0	25
2	WR238605 Succinate	3	25
3	WR238605 Succinate	10	25
4	WR238605 Succinate	30	25
5**	Vitamin A (Retinol Palmitate)	1000 mg/kg/day (250,000 IU/kg/day)	25

\* Presumed Pregnant

\*\* The positive control agent (suspended in water at 200 mg/ml) was administered orally at the specified dose on days 9 and 10 gestation at a dosing volume of 5 ml/kg.

The test article was administered by gavage once daily during gestation days 6 through 15. The gavage procedure was accomplished by the use of a rigid oral feeding needle, and the dosing suspensions were administered at a dosing volume of 5 ml/kg. Dosage formulations were prepared at the beginning of the study. A stock test article suspension was prepared by suspending the appropriate quantity of the test article in the vehicle (aqueous 1% Methylcellulose/0.2% Tween 80). Dosing suspensions for the lower dose levels were prepared by diluting the stock with additional vehicle. The dosing suspensions were kept at 0 - 4°C. Samples of the dosage formulations used at the beginning of the dosing period were analyzed for test article concentration prior to use. Only samples within 10% of their intended concentration were used. The dosage formulations were re-analyzed at the end of the dosing period. A second set of dosage formulations was prepared near the end of the study to dose animals on the last 1 - 4 days of the dosing period (the range was due to the 4 day stagger-start). These formulations were analyzed at the end of the dosing schedule. Stability data obtained from a previous study (UIC/TRL Study No. 047) indicated that the dosing suspensions were stable for two weeks. Homogeneity data obtained from UIC/TRL Study No. 047 also demonstrated that the test article suspensions were homogeneous (coefficients of variation for sampling in the top, middle and bottom of several test suspensions were typically less than 4%).

Non-fasted body weights were recorded on gestation day 0 (GD0 by the supplier), GD5 (for randomization), and on GD6 - 15, GD18 and GD20. Food consumption for all animals was measured during the following intervals: GD6 - 10, GD10 - 15 and GD15 - 20. Clinical signs were observed and recorded approximately 1 - 2 hours post-dosing on the days of dosing and each morning after completion of the dosing period. Animals were also observed for moribundity/mortality immediately prior to dosing and in the afternoon (after at least six hours), and in the afternoon after completion of the dosing period.

On GD20, all rats were killed in random order by carbon dioxide asphyxiation. The abdominal and thoracic cavities were opened by a ventral midline incision, and the contents examined. In gravid animals, the ovaries were examined. The number of *corpora lutea* on each ovary were recorded (ovaries discarded after evaluation). The gravid uteri were examined and weighed. The number and location of viable and nonviable fetuses *in utero*, early and late resorptions and the total number of implantation sites were recorded. A viable fetus was defined as one which responds to stimuli. A non-viable fetus was defined as a term fetus which did not respond to stimuli *in utero* or was not breathing. An early resorption was defined as one in which it is not grossly evident that organogenesis has occurred. A late resorption was defined as one in which it was grossly evident that organogenesis had occurred. A fetus with evident autolysis was considered a late resorption.

The uterine position of each fetus was documented using the following procedure. All implantation sites, including resorptions, were numbered in consecutive fashion beginning with the left distal uterine horn, noting the position of the cervix. Based on gross necropsy observations, a total of 17 maternal spleens in addition to 2 kidneys were saved in 10% neutral buffered formalin, but were not processed for histopathological examination (Section 4.5). Following gross necropsy examination the carcass of each dam was discarded.

The number of fetuses were recorded. Each fetus was weighed and was individually identified noting litter, uterine placement and study number. All fetuses were euthanized by ip injection of a 40% solution of sodium pentobarbital (0.04 ml/fetus). Subsequently, a morphological examination was performed. A detailed examination of each fetus was conducted to include the eyes, palate, head shape and extremities. Any abnormal finding was recorded. One-half of all fetuses from each litter were fixed in Bouin's solution for subsequent soft tissue examination. Following fixation, each fetus was examined using the Wilson free-hand slicing technique (Wilson, 1965). The remaining fetuses in each litter were fixed in alcohol and eviscerated. The skeletons were examined for alterations following staining with Alizarin Red S, and then cleared in glycerin as recommended by Dawson (Dawson, 1926). Skeletal preparations were stored in 99.5% glycerin/0.5% phenol.

### 3.4 Statistical Analyses

Maternal body weights and weight gains, uterine absolute weight, maternal food consumption and mean fetal body weights were analyzed by one-way analysis of variance. If a significant F ratio was obtained ( $p \leq 0.05$ ), Dunnett's test was used for pair-wise comparisons to the vehicle control group.



The incidence of fetal abnormalities was examined in terms of the fetal and litter percentages (% abnormal fetuses/group & % abnormal litters/group). Abnormalities included malformations in addition to variations. The proportions of litters with abnormalities and male to female fetal sex ratios were compared using Fisher's exact test and the Chi-square test, respectively.

Resorptions, non-viable fetuses, viable fetuses, *corpora lutea* (C.L.), implantations, preimplantation loss\*, postimplantation loss\*\*, and total implantation loss\*\*\* were compared using the Kruskal-Wallis test. If a significant effect was seen ( $p \leq 0.05$ ), the Mann-Whitney U test was used for pair-wise comparisons to the vehicle control group.

\*Preimplantation loss% =  $[(\#C.L. - \#implantations)/\# C.L.] \times 100$

\*\*Postimplantation loss% =  $[(\#implantations - \#live\ fetuses)/\#implantations] \times 100$

\*\*\*Total implantation loss% =  $[(\#C.L. - \#live\ fetuses)/\#C.L.] \times 100$

In addition to the written report, summary data tables of parameters and variability were transmitted to the Sponsor on magnetic media (computer diskette) in "ASCII" form. The transcribed data on disk were no longer considered GLP compliant.

#### 4. RESULTS

##### 4.1 Dosage Formulation Analysis

The results of dosage analyses are shown in Table 2. The Analytical Chemistry Report is in Appendix 1. All dosage formulations were within 10% of their target concentration.

##### 4.2 Mortality/Clinical Signs

The summary of clinical signs of toxicity is in Table 3. Individual maternal clinical signs are in Appendix 2.

No animals died during the study. All females were pregnant and the only clinical sign was one incidence of rough coat in each of two animals in the high dose group.

##### 4.3 Maternal Body Weights

The summaries of maternal body weights and weight gains are in Tables 4 and 5, respectively. Individual maternal body weight data are included in Appendix 3.

High dose females (i.e., 30 mg base/kg/day) showed a significant decrease in body weight from GD8 throughout the study. This decrease resulted in a significant decrease in total weight gain. Mid dose animals generally showed significant decreases in body weight from GD12 through GD15 (except on day 13); however, overall weight gain was not significantly less than the vehicle control group. Body weights were unaffected in low dose animals. In the positive control group, a significant decrease in body weight was observed from GD10 to GD20. This resulted in a significant decrease in total weight gain.



#### 4.4 Food Consumption

The summary of mean daily food consumption is in Table 6. Individual maternal food consumption data are shown in Appendix 4.

Food consumption was significantly decreased in the high dose group throughout the study (i.e., GD6 - 20), while animals in the mid dose and positive control groups only showed significant decreases during GD6 to 15. Food consumption was not affected in the low dose group.

#### 4.5 Cesarean-Section and Maternal Gross Observations

The summary of the cesarean section data is in Table 7. The Teratology Report is in Appendix 5.

Enlarged spleens were detected in 16 high dose females (i.e., 30 mg/kg/day) and in one female in the mid dose (i.e., 10 mg/kg/day). In addition, one female in the high dose and one female in the positive control group had hydronephrotic kidneys.

No significant changes in reproductive indices were observed in WR238605-treated animals. A slight, but significant increase in the number of viable fetuses in the low dose in comparison to the control was considered incidental.

Females in the positive control group showed statistically significant decreases in uterine weight and the number of non-viable fetuses. In addition, significant increases in the number of early resorptions and % post-implantation loss were observed.

#### 4.6 Fetal Observations

The summary of fetal observations data is in Table 7. The Teratology report is in Appendix 5.

Fetuses of animals dosed with WR238605 succinate did not show any significant morphologic changes in comparison to the vehicle control group. Fetuses in the positive control group (i.e., retinol palmitate 1000 mg/kg/day on GD9 & 10) showed significant decreases in body weight in both sexes and significant increases in the incidence of several skeletal and visceral anomalies in comparison to the vehicle control group. Salient findings were primarily related to the structures of the head, vertebral column and ribs. In addition, the incidences of four developmental variations, i.e. reduced ossification/unossified skull bones, 14th rudimentary ribs, 14th full ribs and 27 presacral vertebrae, were statistically increased compared to the vehicle control group.

### 5. DISCUSSION

This study evaluated the developmental toxicity of WR238605 Succinate in time-mated CD® female rats. Doses were 0, 3, 10, and 30 mg base/kg/day administered by gavage during GD6 - 15 (GD0 = day of vaginal plug). In addition, a positive control group was administered retinol palmitate, 1000 mg/kg/day on GD9 and 10 by gavage. In high dose animals, maternal

toxic manifestations included rough coat in two animals, significant decreases in body weight from GD8 resulting in significant decreases in total weight gain, and depressed food consumption throughout the study. In the mid dose group, decreases in body weight and daily food consumption were also significant but only during the dosing period. There was also an apparent enlargement of the spleen in 16 females in the high dose and 1 female in the mid dose. Toxic manifestations were not observed in the low dose (i.e., 3 mg base/kg/day). Based on the apparent toxicity at the high and the mid dose, 3 mg base/kg/day was considered the maternal no observable effect level (NOEL).

Fetal toxic manifestations were not seen in WR238605-treated groups, but were observed among the positive control group. These manifestations included significant decreases in fetal body weights and the number of viable fetuses, and significant increases in the incidence of fetuses with skeletal and visceral malformations, primarily related to structures of the head, vertebral column and ribs. Toxicity in the positive control group also included a decrease in uterine weight, an increase in the number of early resorptions and an increase in the % postimplantation loss.

In conclusion, WR238605 succinate was maternally toxic in rats at 10 mg base/kg/day, however developmental toxicity was not observed up to 30 mg base/kg/day, the highest dose tested.

#### 6. REFERENCES

Dawson, AB (1926). A note on the staining of cleared specimens with Alizarin Red S. Stain Technol. 1:123-124.

Wilson, J.G. (1965). Methods for administering drugs and detecting malformations in experimental animals. In: Teratology Principles and Techniques (Wilson, J.G. and Warkany, J., eds.). Un. Chicago Press, pp. 262-277.

#### 7. PERSONNEL

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Reproductive Toxicologist	Ashraf F. Youssef, M.D., Ph.D.
Reproductive Scientist	Roberto A. Matamoros, D.V.M., Ph.D.
Teratologist (PAI)	Michael D. Mercieca, B.S.
Analytical Chemist	Adam Negrusz, Ph.D.
Clinical Veterinarian	James Artwohl, D.V.M., M.S., D.A.C.L.A.M.
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Nancy Dinger, B.S.
Chemistry Specialist	Thomas Tolhurst, B.S.
Quality Assurance	Ronald C. Schoenbeck

Report preparation was assisted by Dr. Ashraf Youssef, Ms. Soudabeh Soura and Ms. Nancy Dinger.

#### 8. ARCHIVES

All raw data, documentation, specimens, test article reserves, and the final report are archived at the Toxicology Research Laboratory, University of Illinois at Chicago, Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612-7353.



Table 1

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

## Summary of Toxic Responses

	WR238605 Succinate				Retinol Palmitate
Dose Level (mg base/kg/day)	4	3	10	30	1000*
Number of Females Pregnant (Non-pregnant)	25(0)	25(0)	25(0)	25(0)	25(0)
Number of Litters (Early termination of pregnancy)	25(0)	25(0)	25(0)	25(0)	25(0)
Clinical Signs (number of females)	-	NE	NE	RC(2)	NE
Decrease in Maternal Body Weight Gain	-	NE	1	-	0
Decrease in Food Consumption	-	NE	1	-	0
Enlarged Spleen (No. animals)	-	0	1	10	0
Hydronephrotic Kidney (No. animals)	-	0	0	1	0
Decrease in Uterine Weight	-	NE	NE	NE	+
Early Resorptions	-	1	1	-	0
Post-implantation Loss	-	1	1	-	+
Decrease in Fetal Body Weight (♀/♂)	-/-	NE/NE	NE/NE	NE/NE	+/+
External Malformations	-	NE	NE	NE	0
Skeletal Malformations	-	NE	NE	NE	0
<b>CONCLUSIONS</b>  This study evaluated the developmental toxicity of WR238605 Succinate in time-mated CD® female rats. Doses were 0, 3, 10, and 30 mg base/kg/day administered by gavage during gestation days (GD) 6 - 15 (GD0 = day of vaginal plug). In addition, a positive control group was administered retinol palmitate, 1000 mg/kg/day, on GD9 and 10 by gavage. Maternal toxicity was observed in the high dose and to a lesser extent in the mid dose. At the high dose, significant decreases in body weight, total weight gain and food consumption were observed throughout the study with rough coat seen in two animals. In addition, enlarged spleen was observed at necropsy in 16 high dose and 1 mid dose females. In the mid dose, marginal decreases in body weight and food consumption were observed during the dosing period. Maternal toxicity was not observed in the low dose. Doses of WR238605 succinate used in the present study were not developmentally toxic. Retinol palmitate (1000 mg/kg/day on GD 9 & 10) was developmentally and maternally toxic. Significant decreases in body weight, total weight gain and uterine weights were observed. In addition, significant increases in fetal malformations and decreases in fetal body weights and the number of viable fetuses were observed. In conclusion, WR238605 succinate was maternally toxic in rats at 10 mg base/kg/day, however developmental toxicity was not observed up to 30 mg base/kg/day, the highest dose level tested.					

+ = Positive effect  
NE = No effect  
? = Possible effect

RC = Rough Coat  
\*mg/kg/day on GD9 & 10



DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

Table 2

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

Dosage Formulation Analyses<sup>a</sup>

Target Concentration (mg base/ml)	Initial (Batch #1)	% Target	Terminal (Batch #1)	% Target	Terminal Batch #2	% Target
0.6	0.65 ± 0.00	108.3	0.66 ± 0.00	110.0	0.60 ± 0.00	100.0
2.0	1.90 ± 0.02	95.0	1.98 ± 0.00	99.0	2.01 ± 0.00	100.5
6.0	6.18 ± 0.02	103.0	6.05 ± 0.03	100.8	6.11 ± 0.02	101.8

<sup>a</sup>Mean ± standard deviation for triplicate runs.

Table 3  
DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

SUMMARY OF CLINICAL SIGNS

STUDY: 154

SEX: FEMALE

DOSE: (mg base/kg/day) GROUP:	0 1-F	3 2-F	10 3-F	30 4-F	1000 (mg/kg/day) <sup>a</sup> 5-F
Scheduled Sacrifice	25	25	25	25	25
Rough Coat	0	0	0	2	0
Total Number of Animals	25	25	25	25	25

<sup>a</sup> Retinol Palmitate given on GD9 and GD10 only

Table 4  
DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

SUMMARY OF BODY WEIGHTS (Grams) (Maternal)

STUDY: 154

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day)	0	3	10	30	1000 (mg/kg/day) <sup>a</sup>
	GROUP:	1-F	2-F	3-F	4-F	5-F
DAY 0	MEAN	213.2	213.4	212.9	212.5	213.2
	S.D.	6.65	5.47	5.20	5.68	5.07
	N	25	25	25	25	25
DAY 5	MEAN	239.6	239.3	239.1	239.3	238.4
	S.D.	9.56	7.27	7.31	9.32	8.60
	N	25	25	25	25	25
DAY 6	MEAN	241.7	239.8	240.9	241.1	240.8
	S.D.	10.73	8.89	7.81	9.18	8.36
	N	25	25	25	25	25
DAY 7	MEAN	243.2	241.8	243.1	239.4	243.9
	S.D.	10.72	7.97	7.95	10.07	10.18
	N	25	25	25	25	25
DAY 8	MEAN	250.7	247.7	245.5	239.3*	247.7
	S.D.	10.23	8.02	9.28	10.43	10.12
	N	25	25	25	25	25
DAY 9	MEAN	256.2	251.7	250.4	241.2*	254.4
	S.D.	9.99	7.56	9.35	11.65	7.58
	N	25	25	25	25	25
DAY 10	MEAN	261.8	258.0	256.8	242.2*	252.1*
	S.D.	10.69	8.52	11.20	11.09	7.60
	N	25	25	25	25	25
DAY 11	MEAN	268.9	263.7	262.3	243.6*	249.2*
	S.D.	10.42	8.15	11.81	11.64	10.44
	N	25	25	25	25	25
DAY 12	MEAN	274.2	269.4	266.1*	245.2*	256.5*
	S.D.	10.32	8.92	14.34	13.73	9.25
	N	25	25	25	25	25
DAY 13	MEAN	279.3	274.8	271.0	244.8*	263.4*
	S.D.	11.55	9.58	14.88	16.58	8.47
	N	25	25	25	25	25

\* P less than .05

Analysis of Variance using DUNNETT'S Procedure

<sup>a</sup> Retinol Palmitate given on GD9 and GD10 only



Table 4 (cont'd)  
DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

SUMMARY OF BODY WEIGHTS (Grams) (Maternal)

STUDY: 154

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day)	0	3	10	30	1000 (mg /kg/day) <sup>a</sup>
	GROUP:	1-F	2-F	3-F	4-F	5-F
DAY 14	MEAN	285.7	280.4	276.1*	244.9*	269.2*
	S.D.	12.03	10.30	14.55	16.65	8.21
	N	25	25	25	25	25
DAY 15	MEAN	293.7	288.3	282.0*	247.8*	277.3*
	S.D.	12.29	11.40	15.03	17.38	9.45
	N	25	25	25	25	25
DAY 18	MEAN	326.0	323.1	317.6	282.8*	307.4*
	S.D.	14.17	13.32	14.45	21.39	14.87
	N	25	25	25	25	25
DAY 20	MEAN	351.3	349.8	343.2	306.6*	330.5*
	S.D.	16.89	16.41	19.19	25.30	19.86
	N	25	25	25	25	25

\* P less than .05

Analysis of Variance using DUNNETT'S Procedure

<sup>a</sup> Retinol Palmitate given on GD9 and GD10 only

Table 5  
DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

SUMMARY OF WEIGHT GAINS (Grams) (Maternal)

STUDY: 154

SEX: FEMALE

PERIOD <sup>a</sup>	DOSE: (mg base/kg/day)	0	3	10	30	1000 (mg/kg/day) <sup>c</sup>
GROUP:		1-F	2-F	3-F	4-F	5-F
DAY 7 <sup>b</sup>	MEAN	1.5	2.0	2.2	-1.7	3.0
	S.D.	9.81	6.74	6.45	4.23	5.19
	N	25	25	25	25	25
DAY 8	MEAN	7.5	5.9	2.4*	-0.2*	3.8*
	S.D.	5.72	4.45	4.37	5.98	3.27
	N	25	25	25	25	25
DAY 9	MEAN	5.4	4.0	4.9	1.9*	6.7
	S.D.	2.83	3.64	3.76	3.87	5.22
	N	25	25	25	25	25
DAY 10	MEAN	5.6	6.3	6.4	1.0*	-2.3*
	S.D.	3.12	3.53	3.13	4.67	6.36
	N	25	25	25	25	25
DAY 11	MEAN	7.1	5.8	5.6	1.3*	-3.0*
	S.D.	2.42	3.11	4.54	6.66	4.80
	N	25	25	25	25	25
DAY 12	MEAN	5.3	5.7	3.8	1.6*	7.4
	S.D.	2.28	3.00	4.57	5.30	6.46
	N	25	25	25	25	25
DAY 13	MEAN	5.1	5.4	4.9	-0.4*	6.9
	S.D.	3.20	2.35	2.89	8.03	4.43
	N	25	25	25	25	25
DAY 14	MEAN	6.4	5.5	5.1	0.2*	5.8
	S.D.	3.11	2.60	3.46	6.73	3.57
	N	25	25	25	25	25
DAY 15	MEAN	8.0	8.0	5.9	2.9*	8.0
	S.D.	3.55	2.91	6.06	4.67	4.18
	N	25	25	25	25	25
DAY 18	MEAN	32.2	34.8	35.6	35.0	30.1
	S.D.	4.20	5.10	5.96	10.83	7.86
	N	25	25	25	25	25

\* P less than .05

Analysis of Variance using DUNNETT'S Procedure

<sup>a</sup> Successive periods

<sup>b</sup> Baseline is day 6

<sup>c</sup> Retinol Palmitate given on GD9 and GD10 only

Table 5 (cont'd)  
DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

SUMMARY OF WEIGHT GAINS (Grams) (Maternal)

STUDY: 154

SEX: FEMALE

PERIOD <sup>a</sup>	DOSE: (mg base/kg/day)	0	3	10	30	1000 (mg/kg/day) <sup>b</sup>
	GROUP:	1-F	2-F	3-F	4-F	5-F
DAY 20	MEAN	25.3	26.6	25.6	23.8	23.1
	S.D.	4.06	5.25	10.12	8.35	9.49
	N	25	25	25	25	25
TOTAL GAIN	MEAN	109.6	109.9	102.3	65.5*	89.6*
	S.D.	13.08	13.84	16.45	23.32	18.06
	N	25	25	25	25	25

\* P less than .05

Analysis of Variance using DUNNETT'S Procedure

<sup>a</sup> Successive periods

<sup>b</sup> Retinol Palmitate given on GD9 and GD10 only



Table 6  
DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 154

SEX: FEMALE

PERIOD <sup>a</sup>	DOSE: (mg base/kg/day) GROUP:	0 1-F	3 2-F	10 3-F	30 4-F	1000 (mg/kg/day) <sup>c</sup> 5-F
DAY 10 <sup>b</sup>	INTAKE (g)	20.2	19.2	17.8*	14.2*	17.3*
	S.D.	1.75	1.53	2.33	2.54	1.59
	N	25	25	25	25	25
DAY 15	INTAKE (g)	22.7	21.1	19.6*	12.7*	18.3*
	S.D.	1.64	1.94	2.80	3.70	1.54
	N	25	25	25	25	25
DAY 20	INTAKE (g)	22.3	21.4	20.9	17.5*	21.7
	S.D.	2.27	2.33	1.91	2.50	2.08
	N	25	25	25	25	25

\* P less than .05

Analysis of Variance using DUNNETT'S Procedure

<sup>a</sup>Inclusive intervals

<sup>b</sup>Food in on day 6

<sup>c</sup>Retinol Palmitate given on GD9 and GD10 only

Table 7

DEVELOPMENTAL TOXICITY (SEGMENT II)  
 STUDY OF WR238605 SUCCINATE IN RATS

## Summary of Cesarean-Section Data and Fetal Evaluations

	WR238605 Succinate				Retinol Palmitate
Dose Level (mg base/kg/day)	0	3	10	30	1000 <sup>a</sup>
Females Pregnant (Non-pregnant)	25(0)	25(0)	25(0)	25(0)	25(0)
Litters (Early termination of pregnancy)	25(0)	25(0)	25(0)	25(0)	25(0)
Uterine Weight (g) <sup>b</sup>	68.66 ± 8.11	74.00 ± 7.79	72.61 ± 8.29	63.47 ± 17.48	58.46 ± 13.59 <sup>c</sup>
Early Resorptions (No.) <sup>b</sup>	0.5 ± 0.8	0.5 ± 0.8	0.7 ± 0.9	0.7 ± 1.0	2.1 ± 2.3 <sup>d</sup>
Viable Fetuses (No.)	12.1 ± 1.6	13.0 ± 1.5 <sup>d</sup>	12.6 ± 1.5	11.5 ± 3.3	10.7 ± 2.4 <sup>d</sup>
Post-implantation Loss (%)	3.9	3.9	5.0	6.4	16.6 <sup>d</sup>
Fetal Body Weight (g) <sup>b</sup> - Males	3.75 ± 0.32	3.83 ± 0.26	3.87 ± 0.25	3.68 ± 0.29	3.32 ± 0.37 <sup>c</sup>
- Females	3.64 ± 0.26	3.68 ± 0.24	3.70 ± 0.23	3.49 ± 0.29	3.13 ± 0.40 <sup>c</sup>
Litters with External Malformations (%)	4(16)	0(0)	0(0)	2(8)	25(100) <sup>a</sup>
Litters with Skeletal Malformations (%)	0(0)	1(4.8)	0(0)	0(0)	17(85) <sup>a</sup>
Total Litters with Malformations (%)	4(16)	1(4)	0(0)	2(8)	25(100) <sup>a</sup>

<sup>a</sup>mg/kg/day on GD9 and GD10

<sup>b</sup>Mean ± S.D.

<sup>c</sup>Statistically significant from vehicle control group using ANOVA/Dunnett's test ( $p \leq 0.05$ )

<sup>d</sup>Statistically significant from vehicle control group using Kruskal-Wallis test ( $p \leq 0.05$ )

<sup>e</sup>Statistically significant from vehicle control group using the Fisher's Exact Test ( $p \leq 0.05$ )

DRAFT

APPENDIX 1

Analytical Chemistry Report



DRAFT

**DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE  
IN RATS**

**UIC/TRL STUDY NUMBER 154**

**Part I: Identity, Purity and Stability Study of WR238605**

**Part II: Dosing Formulations Analysis of WR238605 in 1% Methylcellulose/  
0.2% Tween 80**

**Analysts:** Adam Negrusz  
A. Karl Larsen, Jr.

**Study Site:** Drug Disposition Research Laboratory  
College of Pharmacy  
University of Illinois at Chicago  
Chicago, Illinois 60612

**Sponsor:** Toxicology Research Laboratory  
University of Illinois at Chicago  
Chicago, Illinois 60612

**Report Prepared by:** Dr. Adam Negrusz

**Report Prepared:** January 12, 1995

**Approved:** January 12, 1995  
Dr. Eugene F. Woods, Ph.D.  
Laboratory Director



**Part I: Identity, Purity and Stability Study of WR238605****Objective**

The objective of this study was to confirm the identity, and establish the purity and stability of WR238605.

**Identification****GC-MS System**

Gas Chromatograph:	Hewlett-Packard Model 5890 Series II
Mass Selective Detector:	Hewlett-Packard Model 5970
Analytical Column:	30 m x 0.25 mm ID, DB-1 with a 3 micron film thickness.
GC Parameters:	Injector temp. 250°C, oven temp. 70°C initial, 280°C final, 15°C/minute ramp, carrier gas - helium, flow rate 2 ml/minute, split ratio 10:1

**Procedure**

Subject sample (WR238605 succinate) was submitted by the Toxicology Research Laboratory. The sample was dissolved in hexane:ethanol (4:1) to a concentration of 0.8 µg base/ml and a 2 µl aliquot was injected on the column. The MSD scanned from 40 amu to 475 amu at a rate of 1 scan per second.

**Results - GC-MS**

The mass spectrum indicates a molecular ion m/e 463 ( $M^+$  free base) and m/e 405 [ $M^+$  free base minus  $(CH_2)_3 NH_2$ ]. This pattern is consistent with the structural formula and corresponds to the finding by SRI International (see SRI International Report No. 469, May 9, 1994).

The mass spectrum of the WR238605 sample was previously reported (see Report of UIC/TRL Study No. 097 and Study No. 098 from August 19, 1993) and it is shown in Figure 1.

**Purity****Experimental**

The subject sample (WR238605 succinate) was supplied by the Toxicology Research Laboratory and stored at 4°C ± 2°C when it was not being analyzed.

## Description

A fine powder having a yellow cast and no obvious odor.

## Spectrum

An ultraviolet spectrum (Figure 2) recorded on a Spectra Physics multiwavelength detector interfaced with an IBM Personal Data System 2 was obtained from a 1.2 mg base/ml solution of WR238605 prepared in mobile phase. The sample was found to absorb at 218 and 268 nm.

## HPLC System

Solvent Delivery System:	Perkin-Elmer Series 3B Pump
Injector:	Rheodyne 7125 with 20 $\mu$ l sample loop
Analytical Column:	Bondclone 10 $\mu$ C <sub>18</sub> , 300 mm x 3.9 mm (Phenomenex)
Detector:	Kratos, Spectroflow 773 UV, 268 nm
Integrator:	Perkin-Elmer, LCI-100
Mobile Phase:	9 ml of 85% o-phosphoric acid and 6.8 g of sodium acetate per liter of a mixture of methanol:water (75:25, v/v), flow 1.5 ml/minute

## Procedure

Six solutions of WR238605 were prepared as follows. Twenty five mg of WR238605 succinate sample was weighed into a 25 ml volumetric flask. The sample was dissolved in and the volume brought to mark with mobile phase. A 20  $\mu$ l aliquot of each solution was immediately chromatographed at 268 nm.

## Calculation of Results

Quantitations were based on the assumption of equal detector response per unit weight of all UV-absorbing components. Areas of WR238605 and other detectable components in the subject sample chromatograms were employed in the following equation to calculate the percentage of WR238605 present in the sample:

$$\% \text{PURITY} = (\text{area of WR238605} / \text{total area}) \times 100$$

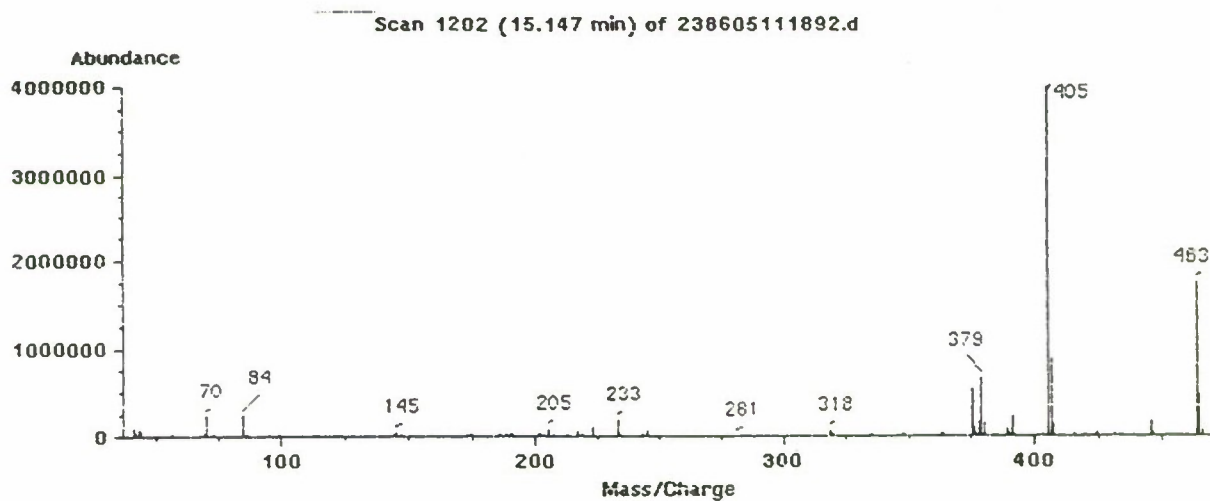


## Results

Typical chromatograms are shown in Figure 3. The subject samples were found to contain less than 1% of one UV-absorbing impurity (268 nm). Percent purity of initial WR238605 sample was found to be 99.91%, standard deviation - 0.06%, terminal 99.94%  $\pm$  0.03%. The assay results are presented in Tables 1 and 2.

DRAFT

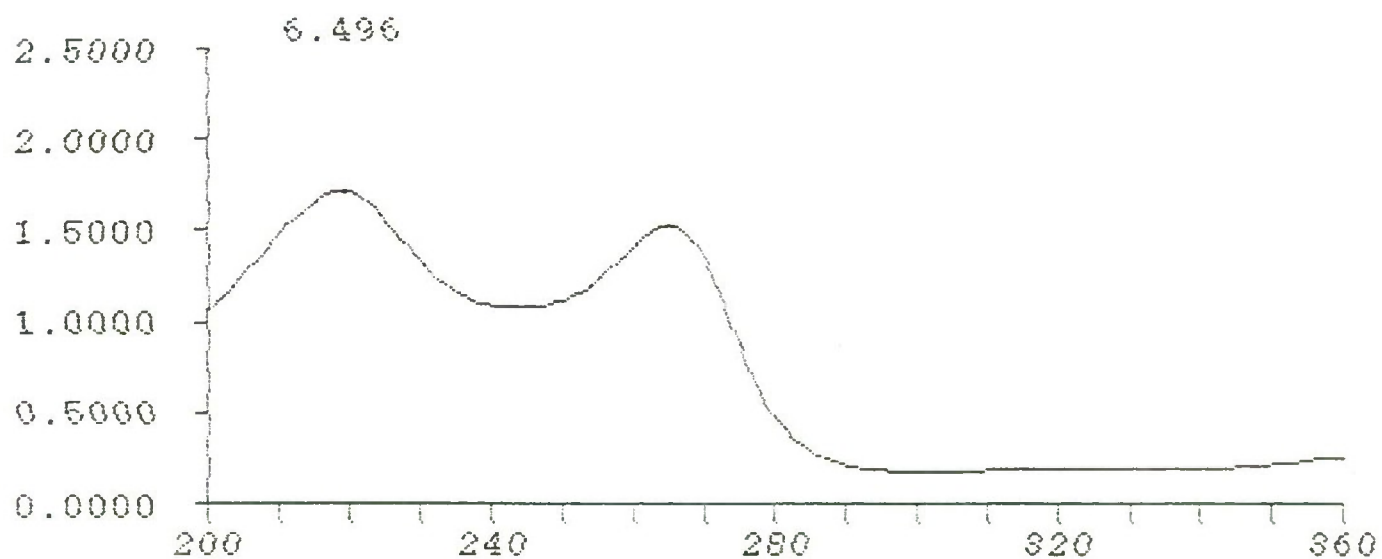
FIGURE 1  
MASS SPECTRUM OF WR238605 SAMPLE



DRAFT

FIGURE 2

ULTRAVIOLET SPECTRUM OF WR238605



Spectra Display: \FOCUS\WR238X.BPF



# DRAFT

FIGURE 3

CHROMATOGRAMS OF WR238605 SAMPLE, CONC. 0.80 MG BASE/ML, 268 NM,  
A - INITIAL SAMPLE, B - TERMINAL SAMPLE

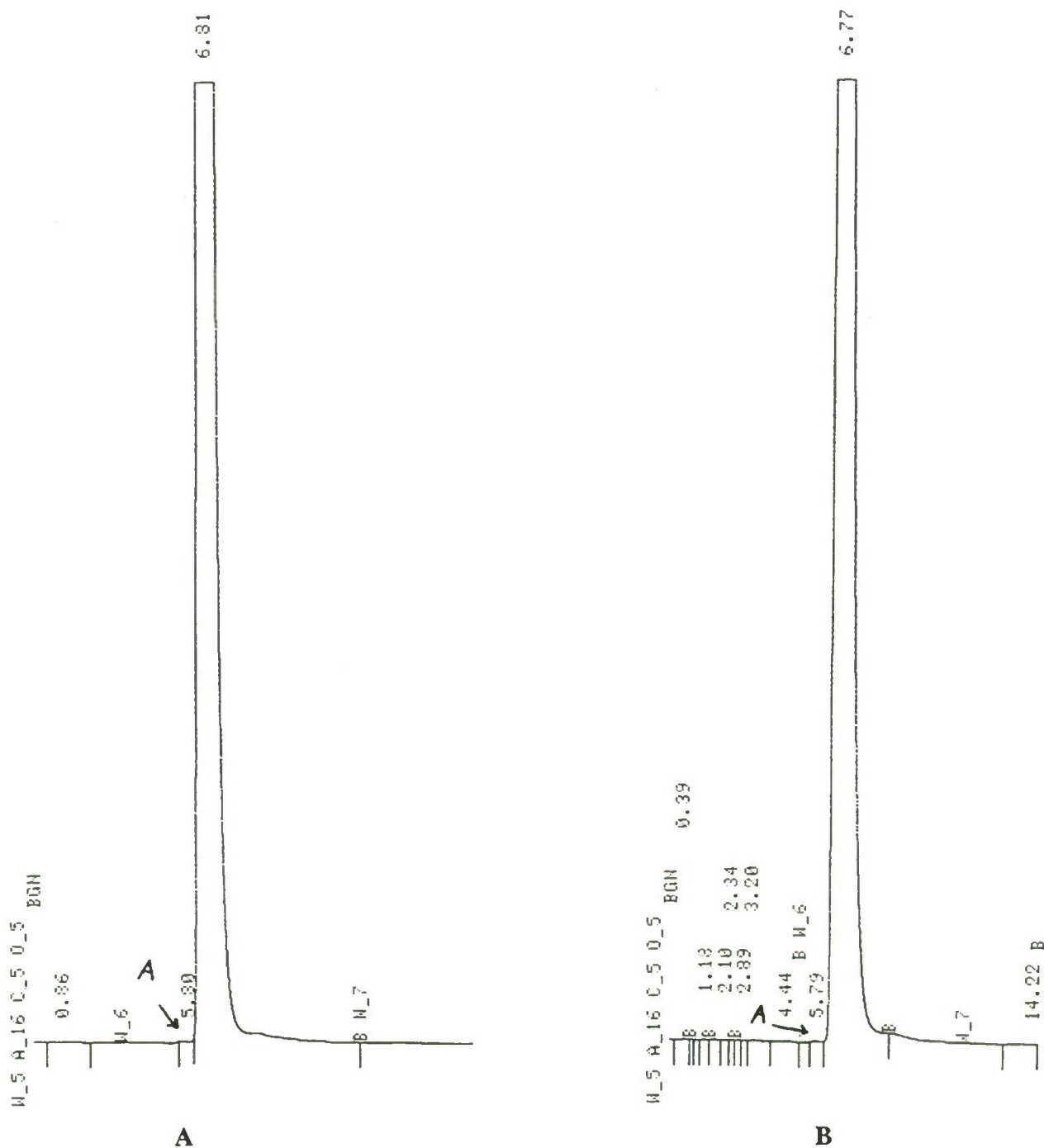


Table 1  
Purity Data for WR238605  
Initial Sample

Solutions

Peak Identity	1	2	3	4	5	6
A	5845	3211	4372	2792	9800	2967
WR238605	20568350	20383974	20512264	20527612	20510750	20548942
Total Area	20579748	20419977	20516636	20543500	20535364	20560364
% Purity	99.94	99.82	99.98	99.92	99.88	99.94

% Purity - 99.91  $\pm$  0.06

DRAFT

Table 2  
Purity Data for WR238605  
Terminal Sample

Solutions

Peak Identity	1	2	3	4	5	6
A	2538	3016	3422	2779	1450	2402
WR238605	20379994	20424860	20440788	20542162	20364232	20464028
Total Area	20398037	20437514	20460042	20547597	20369243	20467969
% Purity	99.91	99.94	99.90	99.97	99.97	99.98

% Purity - 99.94 ± 0.03

DRAFT



**Part II:        Dosing Formulations Analysis of WR238605 in 1% Methylcellulose/0.2% Tween 80**

**Introduction**

Samples from Study No. 154 were submitted by the Toxicology Research Laboratory to the Drug Disposition Research Laboratory for the quantitation of WR238605 in dosing formulations. Samples were received on October 14, 1994 and on October 26, 1994. All samples submitted were analyzed by high performance liquid chromatography by a previously described analytical method (see report UIC/TRL Study No. 098 from August 19, 1993, Part I).

**Results**

Results of dosing formulations for Study No. 154 are found in Table 3. All dosing formulations analyzed were within 10% of their target concentrations.

**DRAFT**

Table 3

Results of Dosing Formulations Analysis for Study No. 154

October 14, 1994

Sample Identification	Target Concentration (mg base/ml)	Mean Concentration ± S.D. (mg base/ml)
WHITE	0	0
YELLOW	0.6	0.6462 ± 0.0018
PINK	2.0	1.8991 ± 0.0169
BLUE	6.0	6.1811 ± 0.0154

October 26, 1994, Batch #1

Sample Identification	Target Concentration (mg base/ml)	Mean Concentration ± S.D. (mg base/ml)
WHITE	0	0
YELLOW	0.6	0.6575 ± 0.0007
PINK	2.0	1.9752 ± 0.0017
BLUE	6.0	6.0453 ± 0.0329

October 26, 1994, Batch #2

Sample Identification	Target Concentration (mg base/ml)	Mean Concentration ± S.D. (mg base/ml)
WHITE	0	0
YELLOW	0.6	0.6004 ± 0.0004
PINK	2.0	2.0106 ± 0.0075
BLUE	6.0	6.1121 ± 0.0174

DRAFT

## APPENDIX 2

### Individual Maternal Clinical Signs



DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 154  
DAY 6-DAY 20

GROUP: 1-F  
DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
346	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
349	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
352	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
357	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
367	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
369	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
381	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
386	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
388	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
396	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
412	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
419	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
421	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 154  
DAY 6-DAY 20

GROUP: 1-F  
DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
428	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
437	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
438	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
451	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
452	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
456	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
467	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
471	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
474	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
497	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
500	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
501	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 154  
DAY 6-DAY 20

GROUP: 2-F  
DOSE: 3 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
350	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
355	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
358	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
360	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
361	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
376	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
393	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
398	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
402	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
403	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
405	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
413	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
415	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 154  
DAY 6-DAY 20

GROUP: 2-F  
DOSE: 3 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
431	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
436	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
439	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
454	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
449	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
462	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
473	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
480	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
481	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
484	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
489	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
495	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20



DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 154  
DAY 6-DAY 20

GROUP: 3-F  
DOSE: 10 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
351	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
371	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
378	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
380	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
383	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
384	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
390	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
395	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
400	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
420	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
424	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
425	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
427	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 154  
DAY 6-DAY 20

GROUP: 3-F  
DOSE: 10 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
434	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
435	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
447	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
453	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
457	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
459	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
469	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
472	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
482	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
486	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
494	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
502	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 154  
DAY 6-DAY 20

GROUP: 4-F  
DOSE: 30 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
354	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
356	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
370	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
374	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
379	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
382	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
385	Normal Normal Rough Coat Scheduled Sacrifice			DAY 6-DAY 9 DAY 11-DAY 19 DAY 10 DAY 20
392	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
399	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
404	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
410	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
417	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 154  
DAY 6-DAY 20

GROUP: 4-F  
DOSE: 30 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
440	Normal Normal Rough Coat Scheduled Sacrifice			DAY 6-DAY 14 DAY 16-DAY 19 DAY 15 DAY 20
441	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
444	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
448	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
450	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
455	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
460	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
475	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
483	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
490	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
491	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20
492	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20



DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 154  
DAY 6-DAY 20

GROUP: 4-F  
DOSE: 30 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
503	Normal Scheduled Sacrifice			DAY 6-DAY 19 DAY 20

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 154  
DAY 6-DAY 20

GROUP: 5-F  
DOSE: 1000 (mg/kg/day)<sup>a</sup>

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
353	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
362	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
364	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
366	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
368	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
372	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
389	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
391	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
401	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
407	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
422	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
423	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
426	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20

<sup>a</sup> Retinol Palmitate given on GD9 and GD10

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 154  
DAY 6-DAY 20

GROUP: 5-F  
DOSE: 1000 (mg/kg/day) <sup>a</sup>

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
430	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
432	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
442	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
445	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
465	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
468	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
476	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
477	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
485	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
493	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
496	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20
499	Normal Scheduled Sacrifice			DAY 9-DAY 19 DAY 20

<sup>a</sup> Retinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 154

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0 1-F	3 2-F	10 3-F	30 4-F	1000 (mg/kg/day) <sup>a</sup> 5-F
DAY 6						
No. Observed		25	25	25	25	0
Normal		25 100%	25 100%	25 100%	25 100%	0
DAY 7						
No. Observed		25	25	25	25	0
Normal		25 100%	25 100%	25 100%	25 100%	0
DAY 8						
No. Observed		25	25	25	25	0
Normal		25 100%	25 100%	25 100%	25 100%	0
DAY 9						
No. Observed		25	25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%	25 100%
DAY 10						
No. Observed		25	25	25	25	25
Normal		25 100%	25 100%	25 100%	24 96%	25 100%
Rough Coat		0	0	0	1 4%	0
DAY 11						
No. Observed		25	25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%	25 100%
DAY 12						
No. Observed		25	25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%	25 100%
DAY 13						
No. Observed		25	25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%	25 100%
DAY 14						
No. Observed		25	25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%	25 100%
DAY 15						
No. Observed		25	25	25	25	25
Normal		25 100%	25 100%	25 100%	24 96%	25 100%

<sup>a</sup> Retinol Palmitate given on GD9 and GD10 only



DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 154

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0 1-F	3 2-F	10 3-F	30 4-F	1000 (mg/kg/day) <sup>a</sup> 5-F
Rough Coat		0	0	0	1 4%	0
DAY 16						
No. Observed		25	25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%	25 100%
DAY 17						
No. Observed		25	25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%	25 100%
DAY 18						
No. Observed		25	25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%	25 100%
DAY 19						
No. Observed		25	25	25	25	25
Normal		25 100%	25 100%	25 100%	25 100%	25 100%
DAY 20						
No. Observed		25	25	25	25	25
Scheduled Sacrifice		25 100%	25 100%	25 100%	25 100%	25 100%

<sup>a</sup> Retinol Palmitate given on GD9 and GD10 only

DRAFT

APPENDIX 3

Individual Maternal Body Weight and Weight Gain Data

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 154

GROUP: 1-F

SEX: FEMALE

DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 0	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
346	208	231	232	219	229	236	241	246	252	257	263	269
349	218	245	248	225	246	251	260	266	270	276	277	283
352	215	242	244	242	256	253	258	267	273	275	281	286
357	222	261	267	261	268	272	277	287	292	299	306	314
367	212	247	249	244	250	257	262	268	268	277	283	286
369	218	252	254	236	258	262	273	278	281	286	293	298
381	217	246	254	244	261	264	266	275	283	284	293	299
386	208	234	232	246	245	251	257	265	268	276	281	288
388	200	231	228	239	238	247	248	260	266	272	283	287
396	217	242	240	252	255	260	266	275	279	286	293	302
412	218	250	244	256	264	269	277	283	289	296	304	310
419	218	244	237	250	251	257	266	271	278	282	287	291
421	205	236	230	240	244	251	254	264	268	274	281	293
428	203	232	235	231	239	243	251	256	260	265	271	275
437	223	239	248	246	254	263	265	270	279	282	287	300
438	206	235	237	243	250	257	256	263	269	276	283	294
451	217	233	241	242	247	250	260	265	267	268	277	284
452	208	244	248	255	260	266	272	277	282	293	294	307
456	219	255	258	261	266	271	281	282	285	294	297	308
467	210	239	246	250	257	266	272	281	284	294	302	312
471	205	220	221	225	230	238	241	248	256	257	261	273
474	216	229	231	239	245	251	257	265	273	277	282	293
497	213	226	231	237	244	247	252	261	267	267	270	286
500	225	244	250	253	259	269	271	281	288	292	300	308
501	210	233	237	244	252	253	262	269	278	277	293	297

MEAN	213	240	242	243	251	256	262	269	274	279	286	294
S.D.	6.6	9.6	10.7	10.7	10.2	10.0	10.7	10.4	10.3	11.5	12.0	12.3
N	25	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 154

GROUP: 1-F

SEX: FEMALE

DOSE: 0 (mg base/kg/day)

ANIMAL # DAY 18 DAY 20

346	298	322
349	309	334
352	326	354
357	350	379
367	316	336
369	332	353
381	333	358
386	316	346
388	323	346
396	339	366
412	343	374
419	322	341
421	327	352
428	306	329
437	337	361
438	326	351
451	313	339
452	342	376
456	336	364
467	343	372
471	306	323
474	324	349
497	314	339
500	348	378
501	320	340

MEAN	326	351
S.D.	14.2	16.9
N	25	25

--: Data Unavailable



DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 154

GROUP: 2-F

SEX: FEMALE

DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY 0	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
350	220	251	256	248	259	260	272	271	279	286	292	299
355	208	239	244	237	242	249	252	257	264	266	271	278
358	210	245	244	238	254	248	260	268	268	274	282	286
360	220	252	255	252	260	265	272	278	289	293	297	309
361	213	242	244	237	251	251	260	263	271	279	286	293
376	218	247	248	239	253	252	259	265	266	272	272	281
393	210	232	227	234	241	238	245	252	262	270	272	278
398	213	247	238	250	247	254	262	265	271	274	279	285
402	209	234	221	237	239	243	250	256	259	265	274	282
403	215	240	243	245	249	253	256	265	272	272	278	284
405	216	242	239	248	249	253	262	273	281	286	295	303
413	221	244	239	252	253	255	260	264	269	272	276	286
415	219	238	226	225	233	244	251	253	260	263	268	277
431	224	242	244	250	254	257	251	258	266	273	280	284
436	210	247	248	253	257	263	269	274	282	290	296	306
439	204	234	236	239	247	251	258	264	272	277	282	294
454	215	244	247	243	250	255	261	267	276	279	279	290
449	212	229	236	234	242	246	254	260	262	269	278	288
462	214	237	243	245	250	255	263	265	271	276	279	293
473	206	228	232	234	240	245	252	255	260	266	270	276
480	204	237	243	249	254	262	270	277	281	291	300	304
481	220	242	246	252	257	262	269	273	274	281	289	300
484	211	231	235	235	238	245	247	260	262	268	276	284
489	214	234	238	241	243	250	254	265	269	277	282	290
495	208	224	224	228	230	236	240	245	249	252	256	258
MEAN	213	239	240	242	248	252	258	264	269	275	280	288
S.D.	5.5	7.3	8.9	8.0	8.0	7.6	8.5	8.1	8.9	9.6	10.3	11.4
N	25	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 154

GROUP: 2-F

SEX: FEMALE

DOSE: 3 (mg base/kg/day)

ANIMAL # DAY 18 DAY 20

350	329	355
355	322	349
358	319	346
360	342	374
361	332	358
376	312	342
393	310	340
398	322	339
402	324	350
403	309	322
405	341	366
413	319	349
415	310	329
431	327	351
436	341	366
439	331	366
454	328	358
449	320	351
462	326	351
473	304	329
480	346	383
481	337	367
484	309	335
489	327	355
495	291	313

MEAN	323	350
S.D.	13.3	16.4
N	25	25

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 154

GROUP: 3-F

SEX: FEMALE

DOSE: 10 (mg base/kg/day)

ANIMAL #	DAY 0	OAY 5	OAY 6	OAY 7	OAY 8	OAY 9	DAY 10	OAY 11	OAY 12	OAY 13	OAY 14	OAY 15
351	216	247	248	250	249	253	260	266	273	276	283	287
371	220	253	260	258	261	269	280	280	290	292	294	302
378	216	243	247	248	253	256	264	268	268	277	277	281
380	219	248	248	251	254	254	262	267	271	277	286	291
383	210	238	236	239	237	239	245	249	253	256	262	269
384	211	245	247	227	231	236	238	244	252	262	267	276
390	208	239	246	239	247	250	260	263	271	272	275	284
395	216	248	248	251	254	263	271	277	280	288	294	296
400	205	235	239	239	239	244	249	260	263	271	278	284
420	206	229	232	236	238	242	249	253	258	262	266	269
424	210	241	243	244	244	249	256	263	263	266	271	252
425	225	245	249	248	254	255	263	266	271	277	279	290
427	218	241	248	251	258	263	269	280	284	294	299	306
434	213	234	240	239	248	241	244	254	259	262	268	272
435	214	238	240	246	248	255	255	263	267	270	281	289
447	219	245	236	255	260	267	278	282	286	289	300	304
453	216	245	241	247	250	258	265	272	273	280	278	288
457	206	231	235	236	237	242	246	255	255	260	264	273
459	208	237	239	243	244	251	263	271	278	282	289	298
469	208	228	228	230	231	238	239	249	253	261	261	269
472	213	241	241	246	233	246	250	257	266	267	274	284
482	206	224	226	231	229	237	244	232	218	220	231	245
486	215	240	242	248	251	256	258	265	271	276	283	291
494	210	230	230	236	242	249	256	262	265	273	274	282
502	214	232	234	239	245	247	255	260	264	265	269	269
MEAN	213	239	241	243	245	250	257	262	266	271	276	282
S.D.	5.2	7.3	7.8	7.9	9.3	9.3	11.2	11.8	14.3	14.9	14.5	15.0
N	25	25	25	25	25	25	25	25	25	25	25	25

---: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 154

GROUP: 3-F

SEX: FEMALE

DOSE: 10 (mg base/kg/day)

ANIMAL # DAY 18 DAY 20

351	318	350
371	340	380
378	318	351
380	327	355
383	296	318
384	315	343
390	319	308
395	338	355
400	325	353
420	308	337
424	308	321
425	322	345
427	340	374
434	310	343
435	316	330
447	337	371
453	319	351
457	313	340
459	332	368
469	297	322
472	319	343
482	282	311
486	327	349
494	314	342
502	300	321

MEAN	318	343
S.D.	14.5	19.2
N	25	25

--: Data Unavailable



DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 154

GROUP: 4-F

SEX: FEMALE

DOSE: 30 (mg base/kg/day)

ANIMAL #	DAY 0	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
354	216	254	257	260	257	260	264	269	271	272	268	275
356	215	250	252	251	248	249	245	246	253	254	257	260
370	216	243	248	249	253	247	246	255	245	247	251	257
374	218	243	243	243	239	236	244	248	245	228	235	238
379	209	239	243	228	235	233	229	235	232	230	219	212
382	211	247	249	249	249	251	253	255	264	265	268	269
385	210	234	234	231	222	224	223	225	214	214	215	227
392	213	239	247	243	243	251	241	242	248	251	254	255
399	200	230	231	235	237	241	245	252	255	259	258	262
404	224	249	252	253	251	257	262	264	263	269	268	271
410	207	244	247	249	234	232	243	246	257	269	268	268
417	216	241	243	242	241	246	248	247	250	251	247	247
440	220	259	252	252	252	259	256	238	245	253	256	258
441	210	239	236	232	221	227	226	236	234	236	239	254
444	213	237	238	236	240	239	239	241	242	238	231	233
448	208	232	237	235	240	242	242	246	244	235	236	243
450	215	241	244	243	247	248	245	248	250	247	225	227
455	214	244	243	241	246	251	249	254	258	258	260	266
460	218	228	227	228	233	232	229	221	224	230	237	237
475	215	236	239	235	225	219	227	234	234	244	246	246
483	219	247	250	239	247	254	252	253	261	260	254	260
490	211	232	234	234	240	240	244	238	244	234	242	240
491	203	217	219	216	220	223	226	230	229	231	234	238
492	206	230	232	227	228	230	234	237	237	212	212	214
503	205	228	231	235	234	239	244	229	230	232	243	238
MEAN	212	239	241	239	239	241	242	244	245	245	245	248
S.D.	5.7	9.3	9.2	10.1	10.4	11.7	11.1	11.6	13.7	16.6	16.7	17.4
N	25	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 154

GROUP: 4-F

SEX: FEMALE

DOSE: 30(mg base/kg/day)

ANIMAL # DAY 18 DAY 20

354	303	327
356	304	325
370	280	317
374	280	308
379	235	250
382	303	318
385	267	282
392	307	330
399	306	331
404	304	326
410	325	360
417	278	303
440	286	310
441	297	326
444	269	290
448	261	289
450	270	267
455	277	294
460	275	297
475	277	310
483	310	346
490	263	288
491	275	306
492	247	270
503	271	295

MEAN	283	307
S.D.	21.4	25.3
N	25	25

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 154

GROUP: 5-F  
DOSE: 1000(mg/kg/day)<sup>a</sup>

SEX: FEMALE

ANIMAL #	DAY 0	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
353	215	246	247	252	250	262	258	257	269	273	275	287
362	220	254	249	255	256	263	254	246	255	267	271	280
364	209	241	243	242	242	249	248	246	254	266	268	275
366	211	249	248	252	250	257	260	263	264	271	272	280
368	219	245	248	249	254	256	257	258	269	271	277	285
372	217	241	244	243	249	250	253	255	257	270	269	278
389	209	245	246	249	251	257	255	259	262	264	266	271
391	212	238	244	245	250	256	254	255	262	271	276	284
401	219	243	246	259	264	267	243	236	247	255	263	279
407	205	225	231	232	239	245	244	235	249	251	256	259
422	214	233	244	240	248	254	254	258	256	260	262	268
423	218	247	253	253	263	266	269	271	273	274	280	292
426	216	230	233	236	242	250	247	239	250	253	259	274
430	213	237	236	247	248	258	245	246	249	261	273	284
432	214	240	239	248	250	259	255	255	272	276	281	291
442	211	239	241	247	253	254	259	254	255	267	275	286
445	220	250	256	256	261	265	267	267	263	270	279	286
465	211	234	242	244	243	247	248	244	241	246	255	261
468	204	226	227	233	233	242	237	234	244	251	255	267
476	204	235	240	246	252	260	254	246	261	265	279	282
477	220	229	244	243	246	253	250	239	254	263	273	274
485	217	246	224	212	216	244	252	240	241	259	268	271
493	207	223	229	232	238	241	240	238	247	253	260	259
496	215	239	240	250	255	260	254	249	264	272	276	285
499	209	225	227	232	240	246	246	239	255	256	263	274
MEAN	213	238	241	244	248	254	252	249	257	263	269	277
S.D.	5.1	8.6	8.4	10.2	10.1	7.6	7.6	10.4	9.2	8.5	8.2	9.4
N	25	25	25	25	25	25	25	25	25	25	25	25

---: Data Unavailable

<sup>a</sup> Retinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 154

GROUP: 5-F  
DOSE: 1000 (mg/kg/day)<sup>a</sup> SEX: FEMALE

ANIMAL # DAY 18 DAY 20

353	326	346
362	313	304
364	307	327
366	311	333
368	321	346
372	304	330
389	308	319
391	315	342
401	309	324
407	292	309
422	306	329
423	320	349
426	300	325
430	318	350
432	327	365
442	313	341
445	321	357
465	284	304
468	281	302
476	305	340
477	299	328
485	305	330
493	268	281
496	331	356
499	300	325

MEAN	307	330
S.D.	14.9	19.9
N	25	25

--: Data Unavailable

<sup>a</sup> Retinol Palmitate given on GD9 and GD10 only



DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)<sup>a</sup>

STUDY: 154

GROUP: 1-F  
DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	DAY 7 <sup>c</sup>	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 18	DAY 20
346	-13.0	10.0	7.0	5.0	5.0	6.0	5.0	6.0	6.0	29.0	24.0
349	-23.0	21.0	5.0	9.0	6.0	4.0	6.0	1.0	6.0	26.0	25.0
352	-2.0	14.0	-3.0	5.0	9.0	6.0	2.0	6.0	5.0	40.0	28.0
357	-6.0	7.0	4.0	5.0	10.0	5.0	7.0	7.0	8.0	36.0	29.0
367	-5.0	6.0	7.0	5.0	6.0	0.0	9.0	6.0	3.0	30.0	20.0
369	-18.0	22.0	4.0	11.0	5.0	3.0	5.0	7.0	5.0	34.0	21.0
381	-10.0	17.0	3.0	2.0	9.0	8.0	1.0	9.0	6.0	34.0	25.0
386	14.0	-1.0	6.0	6.0	8.0	3.0	8.0	5.0	7.0	28.0	30.0
388	11.0	-1.0	9.0	1.0	12.0	6.0	6.0	11.0	4.0	36.0	23.0
396	12.0	3.0	5.0	6.0	9.0	4.0	7.0	7.0	9.0	37.0	27.0
412	12.0	8.0	5.0	8.0	6.0	6.0	7.0	8.0	6.0	33.0	31.0
419	13.0	1.0	6.0	9.0	5.0	7.0	4.0	5.0	4.0	31.0	19.0
421	10.0	4.0	7.0	3.0	10.0	4.0	6.0	7.0	12.0	34.0	25.0
428	-4.0	8.0	4.0	8.0	5.0	4.0	5.0	6.0	4.0	31.0	23.0
437	-2.0	8.0	9.0	2.0	5.0	9.0	3.0	5.0	13.0	37.0	24.0
438	6.0	7.0	7.0	-1.0	7.0	6.0	7.0	7.0	11.0	32.0	25.0
451	1.0	5.0	3.0	10.0	5.0	2.0	1.0	9.0	7.0	29.0	26.0
452	7.0	5.0	6.0	6.0	5.0	5.0	11.0	1.0	13.0	35.0	34.0
456	3.0	5.0	5.0	10.0	1.0	3.0	9.0	3.0	11.0	28.0	28.0
467	4.0	7.0	9.0	6.0	9.0	3.0	10.0	8.0	10.0	31.0	29.0
471	4.0	5.0	8.0	3.0	7.0	8.0	1.0	4.0	12.0	33.0	17.0
474	8.0	6.0	6.0	6.0	8.0	8.0	4.0	5.0	11.0	31.0	25.0
497	6.0	7.0	3.0	5.0	9.0	6.0	0.0	3.0	16.0	28.0	25.0
500	3.0	6.0	10.0	2.0	10.0	7.0	4.0	8.0	8.0	40.0	30.0
501	7.0	8.0	1.0	9.0	7.0	9.0	-1.0	16.0	4.0	23.0	20.0
MEAN	1.5	7.5	5.4	5.6	7.1	5.3	5.1	6.4	8.0	32.2	25.3
S.D.	9.81	5.72	2.83	3.12	2.42	2.28	3.20	3.11	3.55	4.20	4.06
N	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable      b: Scheduled Sacrifice

<sup>a</sup>Successive periods

<sup>c</sup>Baseline is day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)<sup>a</sup>

STUDY: 154

GROUP: 2-F

SEX: FEMALE

DOSE: 3 (mg base/kg/day)

ANIMAL #	DAY 7 <sup>c</sup>	OAY 8	OAY 9	OAY 10	OAY 11	OAY 12	OAY 13	OAY 14	OAY 15	DAY 18	OAY 20
350	-8.0	11.0	1.0	12.0	-1.0	8.0	7.0	6.0	7.0	30.0	26.0
355	-7.0	5.0	7.0	3.0	5.0	7.0	2.0	5.0	7.0	44.0	27.0
358	-6.0	16.0	-6.0	12.0	8.0	0.0	6.0	8.0	4.0	33.0	27.0
360	-3.0	8.0	5.0	7.0	6.0	11.0	4.0	4.0	12.0	33.0	32.0
361	-7.0	14.0	0.0	9.0	3.0	8.0	8.0	7.0	7.0	39.0	26.0
376	-9.0	14.0	-1.0	7.0	6.0	1.0	6.0	0.0	9.0	31.0	30.0
393	7.0	7.0	-3.0	7.0	7.0	10.0	8.0	2.0	6.0	32.0	30.0
398	12.0	-3.0	7.0	8.0	3.0	6.0	3.0	5.0	6.0	37.0	17.0
402	16.0	2.0	4.0	7.0	6.0	3.0	6.0	9.0	8.0	42.0	26.0
403	2.0	4.0	4.0	3.0	9.0	7.0	0.0	6.0	6.0	25.0	13.0
405	9.0	1.0	4.0	9.0	11.0	8.0	5.0	9.0	8.0	38.0	25.0
413	13.0	1.0	2.0	5.0	4.0	5.0	3.0	4.0	10.0	33.0	30.0
415	-1.0	8.0	11.0	7.0	2.0	7.0	3.0	5.0	9.0	33.0	19.0
431	6.0	4.0	3.0	-6.0	7.0	8.0	7.0	7.0	4.0	43.0	24.0
436	5.0	4.0	6.0	6.0	5.0	8.0	8.0	6.0	10.0	35.0	25.0
439	3.0	8.0	4.0	7.0	6.0	8.0	5.0	5.0	12.0	37.0	35.0
454	-4.0	7.0	5.0	6.0	6.0	9.0	3.0	0.0	11.0	38.0	30.0
449	-2.0	8.0	4.0	8.0	6.0	2.0	7.0	9.0	10.0	32.0	31.0
462	2.0	5.0	5.0	8.0	2.0	6.0	5.0	3.0	14.0	33.0	25.0
473	2.0	6.0	5.0	7.0	3.0	5.0	6.0	4.0	6.0	28.0	25.0
480	6.0	5.0	8.0	8.0	7.0	4.0	10.0	9.0	4.0	42.0	37.0
481	6.0	5.0	5.0	7.0	4.0	1.0	7.0	8.0	11.0	37.0	30.0
484	0.0	3.0	7.0	2.0	13.0	2.0	6.0	8.0	8.0	25.0	26.0
489	3.0	2.0	7.0	4.0	11.0	4.0	8.0	5.0	8.0	37.0	28.0
495	4.0	2.0	6.0	4.0	5.0	4.0	3.0	4.0	2.0	33.0	22.0
MEAN	2.0	5.9	4.0	6.3	5.8	5.7	5.4	5.5	8.0	34.8	26.6
S.D.	6.74	4.45	3.64	3.53	3.11	3.00	2.35	2.60	2.91	5.10	5.25
N	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

b: Scheduled Sacrifice

<sup>a</sup>Successive periods

<sup>c</sup>Baseline is day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)<sup>a</sup>

STUDY: 154

GROUP: 3-F

SEX: FEMALE

DOSE: 10 (mg base/kg/day)

ANIMAL #	DAY 7 <sup>c</sup>	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 18	DAY 20
351	2.0	-1.0	4.0	7.0	6.0	7.0	3.0	7.0	4.0	31.0	32.0
371	-2.0	3.0	8.0	11.0	0.0	10.0	2.0	2.0	8.0	38.0	40.0
378	1.0	5.0	3.0	8.0	4.0	0.0	9.0	0.0	4.0	37.0	33.0
380	3.0	3.0	0.0	8.0	5.0	4.0	6.0	9.0	5.0	36.0	28.0
383	3.0	-2.0	2.0	6.0	4.0	4.0	3.0	6.0	7.0	27.0	22.0
384	-20.0	4.0	5.0	2.0	6.0	8.0	10.0	5.0	9.0	39.0	28.0
390	-7.0	8.0	3.0	10.0	3.0	8.0	1.0	3.0	9.0	35.0	-11.0
395	3.0	3.0	9.0	8.0	6.0	3.0	8.0	6.0	2.0	42.0	17.0
400	0.0	0.0	5.0	5.0	11.0	3.0	8.0	7.0	6.0	41.0	28.0
420	4.0	2.0	4.0	7.0	4.0	5.0	4.0	4.0	3.0	39.0	29.0
424	1.0	0.0	5.0	7.0	7.0	0.0	3.0	5.0	-19.0	56.0	13.0
425	-1.0	6.0	1.0	8.0	3.0	5.0	6.0	2.0	11.0	32.0	23.0
427	3.0	7.0	5.0	6.0	11.0	4.0	10.0	5.0	7.0	34.0	34.0
434	-1.0	9.0	-7.0	3.0	10.0	5.0	3.0	6.0	4.0	38.0	33.0
435	6.0	2.0	7.0	0.0	8.0	4.0	3.0	11.0	8.0	27.0	14.0
447	19.0	5.0	7.0	11.0	4.0	4.0	3.0	11.0	4.0	33.0	34.0
453	6.0	3.0	8.0	7.0	7.0	1.0	7.0	-2.0	10.0	31.0	32.0
457	1.0	1.0	5.0	4.0	9.0	0.0	5.0	4.0	9.0	40.0	27.0
459	4.0	1.0	7.0	12.0	8.0	7.0	4.0	7.0	9.0	34.0	36.0
469	2.0	1.0	7.0	1.0	10.0	4.0	8.0	0.0	8.0	28.0	25.0
472	5.0	-13.0	13.0	4.0	7.0	9.0	1.0	7.0	10.0	35.0	24.0
482	5.0	-2.0	8.0	7.0	-12.0	-14.0	2.0	11.0	14.0	37.0	29.0
486	6.0	3.0	5.0	2.0	7.0	6.0	5.0	7.0	8.0	36.0	22.0
494	6.0	6.0	7.0	7.0	6.0	3.0	8.0	1.0	8.0	32.0	28.0
502	5.0	6.0	2.0	8.0	5.0	4.0	1.0	4.0	0.0	31.0	21.0
MEAN	2.2	2.4	4.9	6.4	5.6	3.8	4.9	5.1	5.9	35.6	25.6
S.D.	6.45	4.37	3.76	3.13	4.54	4.57	2.89	3.46	6.06	5.96	10.12
N	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

b: Scheduled Sacrifice

<sup>a</sup>Successive periods

<sup>c</sup>Baseline is day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams)<sup>a</sup>

STUDY: 154

GROUP: 4-F

SEX: FEMALE

DOSE: 30 (mg base/kg/day)

ANIMAL #	OAY 7 <sup>c</sup>	OAY 8	OAY 9	OAY 10	DAY 11	DAY 12	OAY 13	OAY 14	DAY 15	OAY 18	DAY 20
354	3.0	-3.0	3.0	4.0	5.0	2.0	1.0	-4.0	7.0	28.0	24.0
356	-1.0	-3.0	1.0	-4.0	1.0	7.0	1.0	3.0	3.0	44.0	21.0
370	1.0	4.0	-6.0	-1.0	9.0	-10.0	2.0	4.0	6.0	23.0	37.0
374	0.0	-4.0	-3.0	8.0	4.0	-3.0	-17.0	7.0	3.0	42.0	28.0
379	-15.0	7.0	-2.0	-4.0	6.0	-3.0	-2.0	-11.0	-7.0	23.0	15.0
382	0.0	0.0	2.0	2.0	2.0	9.0	1.0	3.0	1.0	34.0	15.0
385	-3.0	-9.0	2.0	-1.0	2.0	-11.0	0.0	1.0	12.0	40.0	15.0
392	-4.0	0.0	8.0	-10.0	1.0	6.0	3.0	3.0	1.0	52.0	23.0
399	4.0	2.0	4.0	4.0	7.0	3.0	4.0	-1.0	4.0	44.0	25.0
404	1.0	-2.0	6.0	5.0	2.0	-1.0	6.0	-1.0	3.0	33.0	22.0
410	2.0	-15.0	-2.0	11.0	3.0	11.0	12.0	-1.0	0.0	57.0	35.0
417	-1.0	-1.0	5.0	2.0	-1.0	3.0	1.0	-4.0	0.0	31.0	25.0
440	0.0	0.0	7.0	-3.0	-18.0	7.0	8.0	3.0	2.0	28.0	24.0
441	-4.0	-11.0	6.0	-1.0	10.0	-2.0	2.0	3.0	15.0	43.0	29.0
444	-2.0	4.0	-1.0	0.0	2.0	1.0	-4.0	-7.0	2.0	36.0	21.0
448	-2.0	5.0	2.0	0.0	4.0	-2.0	-9.0	1.0	7.0	18.0	28.0
450	-1.0	4.0	1.0	-3.0	3.0	2.0	-3.0	-22.0	2.0	43.0	-3.0
455	-2.0	5.0	5.0	-2.0	5.0	4.0	0.0	2.0	6.0	11.0	17.0
460	1.0	5.0	-1.0	-3.0	-8.0	3.0	6.0	7.0	0.0	38.0	22.0
475	-4.0	-10.0	-6.0	8.0	7.0	0.0	10.0	2.0	0.0	31.0	33.0
483	-11.0	8.0	7.0	-2.0	1.0	8.0	-1.0	-6.0	6.0	50.0	36.0
490	0.0	6.0	0.0	4.0	-6.0	6.0	-10.0	8.0	-2.0	23.0	25.0
491	-3.0	4.0	3.0	3.0	4.0	-1.0	2.0	3.0	4.0	37.0	31.0
492	-5.0	1.0	2.0	4.0	3.0	0.0	-25.0	0.0	2.0	33.0	23.0
503	4.0	-1.0	5.0	5.0	-15.0	1.0	2.0	11.0	-5.0	33.0	24.0
MEAN	-1.7	-0.2	1.9	1.0	1.3	1.6	-0.4	0.2	2.9	35.0	23.8
S.D.	4.23	5.98	3.87	4.67	6.66	5.30	8.03	6.73	4.67	10.83	8.35
N	25	25	25	25	25	25	25	25	25	25	25

---: Data Unavailable

b: Scheduled Sacrifice

<sup>a</sup>Successive periods

<sup>c</sup>Baseline is day 6



DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL WEIGHT GAIN (Grams) <sup>a</sup>

STUDY: 154

GROUP: 5-F

SEX: FEMALE

DOSE: 1000 (mg /kg/day) <sup>d</sup>

ANIMAL #	DAY 7 <sup>c</sup>	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 18	DAY 20
353	5.0	-2.0	12.0	-4.0	-1.0	12.0	4.0	2.0	12.0	39.0	20.0
362	6.0	1.0	7.0	-9.0	-8.0	9.0	12.0	4.0	9.0	33.0	-9.0
364	-1.0	0.0	7.0	-1.0	-2.0	8.0	12.0	2.0	7.0	32.0	20.0
366	4.0	-2.0	7.0	3.0	3.0	1.0	7.0	1.0	8.0	31.0	22.0
368	1.0	5.0	2.0	1.0	1.0	11.0	2.0	6.0	8.0	36.0	25.0
372	-1.0	6.0	1.0	3.0	2.0	2.0	13.0	-1.0	9.0	26.0	26.0
389	3.0	2.0	6.0	-2.0	4.0	3.0	2.0	2.0	5.0	37.0	11.0
391	1.0	5.0	6.0	-2.0	1.0	7.0	9.0	5.0	8.0	31.0	27.0
401	13.0	5.0	3.0	-24.0	-7.0	11.0	8.0	8.0	16.0	30.0	15.0
407	1.0	7.0	6.0	-1.0	-9.0	14.0	2.0	5.0	3.0	33.0	17.0
422	-4.0	8.0	6.0	0.0	4.0	-2.0	4.0	2.0	6.0	38.0	23.0
423	0.0	10.0	3.0	3.0	2.0	2.0	1.0	6.0	12.0	28.0	29.0
426	3.0	6.0	8.0	-3.0	-8.0	11.0	3.0	6.0	15.0	26.0	25.0
430	11.0	1.0	10.0	-13.0	1.0	3.0	12.0	12.0	11.0	34.0	32.0
432	9.0	2.0	9.0	-4.0	0.0	17.0	4.0	5.0	10.0	36.0	38.0
442	6.0	6.0	1.0	5.0	-5.0	1.0	12.0	8.0	11.0	27.0	28.0
445	0.0	5.0	4.0	2.0	0.0	-4.0	7.0	9.0	7.0	35.0	36.0
465	2.0	-1.0	4.0	1.0	-4.0	-3.0	5.0	9.0	6.0	23.0	20.0
468	6.0	0.0	9.0	-5.0	-3.0	10.0	7.0	4.0	12.0	14.0	21.0
476	6.0	6.0	8.0	-6.0	-8.0	15.0	4.0	14.0	3.0	23.0	35.0
477	-1.0	3.0	7.0	-3.0	-11.0	15.0	9.0	10.0	1.0	25.0	29.0
485	-12.0	4.0	28.0	8.0	-12.0	1.0	18.0	9.0	3.0	34.0	25.0
493	3.0	6.0	3.0	-1.0	-2.0	9.0	6.0	7.0	-1.0	9.0	13.0
496	10.0	5.0	5.0	-6.0	-5.0	15.0	8.0	4.0	9.0	46.0	25.0
499	5.0	8.0	6.0	0.0	-7.0	16.0	1.0	7.0	11.0	26.0	25.0
MEAN	3.0	3.8	6.7	-2.3	-3.0	7.4	6.9	5.8	8.0	30.1	23.1
S.D.	5.19	3.27	5.22	6.36	4.80	6.46	4.43	3.57	4.18	7.86	9.49
N	25	25	25	25	25	25	25	25	25	25	25

--: Data Unavailable

b: Scheduled Sacrifice

<sup>a</sup> Successive periods

<sup>c</sup> Baseline is day 6

<sup>d</sup> Retinol Palmitate given on GD9 and GD10 only

DRAFT

APPENDIX 4

Individual Maternal Food Consumption Data

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams) <sup>a</sup>

STUDY: 154

GROUP: 1-F

SEX: FEMALE

DOSE: 0 (mg base/kg/day)

ANIMAL # DAY 10 <sup>b</sup> DAY 15 DAY 20

346	17.0	22.4	20.0
349	18.0	21.0	20.4
352	20.3	22.8	23.6
357	21.0	24.4	24.4
367	17.5	21.4	23.2
369	18.5	23.0	24.0
381	22.0	24.8	23.0
386	19.5	22.0	22.6
388	21.3	25.2	25.0
396	19.8	22.4	25.2
412	21.3	23.6	23.8
419	19.5	21.0	22.8
421	20.3	22.0	22.0
428	19.8	23.8	17.8
437	20.3	23.0	23.8
438	18.5	21.4	22.6
451	19.3	20.8	21.6
452	23.8	24.6	25.8
456	21.8	22.6	22.4
467	22.8	27.0	23.0
471	17.3	19.8	19.6
474	21.5	22.2	21.2
497	20.3	20.8	20.0
500	22.3	23.4	24.2
501	20.3	23.0	16.6

MEAN	20.2	22.7	22.3
S.D.	1.75	1.64	2.27
N	25	25	25

--: Data Unavailable

<sup>a</sup>Inclusive intervals

<sup>b</sup>Food in on day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DATA

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)<sup>a</sup>

STUDY: 154

GROUP: 2-F  
DOSE: 3 (mg base/kg/day)

SEX: FEMALE

ANIMAL # DAY 10<sup>b</sup> DAY 15 DAY 20

350	17.5	21.8	22.0
355	18.5	19.6	21.0
358	19.3	20.0	20.8
360	19.0	21.6	22.8
361	19.5	24.0	23.4
376	19.3	21.2	22.2
393	16.5	19.4	19.4
398	18.5	19.4	20.4
402	19.0	20.6	22.2
403	21.0	18.6	19.2
405	20.5	23.8	23.0
413	18.8	19.8	20.4
415	16.0	19.8	21.4
431	19.0	20.0	20.8
436	20.0	24.4	24.4
439	22.3	22.8	23.4
454	20.0	22.4	23.0
449	19.5	20.6	22.4
462	19.0	21.0	20.6
473	20.5	19.6	17.6
480	21.0	23.2	24.4
481	21.3	20.6	24.4
484	18.8	22.0	22.0
489	16.5	24.8	14.2
495	18.0	17.0	18.8
MEAN	19.2	21.1	21.4
S.D.	1.53	1.94	2.33
N	25	25	25

--: Data Unavailable

<sup>a</sup>Inclusive intervals

<sup>b</sup>Food in on day 6



DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)<sup>a</sup>

STUDY: 154

GROUP: 3-F

SEX: FEMALE

DOSE: 1.0 (mg base/kg/day)

ANIMAL # DAY 10<sup>b</sup> DAY 15 DAY 20

351	16.8	19.6	19.6
371	17.5	20.4	23.8
378	17.0	17.0	20.8
380	17.8	22.8	21.6
383	15.0	14.0	20.8
384	11.3	20.6	21.4
390	16.8	18.6	19.0
395	19.8	21.0	22.4
400	17.3	21.6	23.8
420	19.3	18.0	18.2
424	18.0	16.4	19.0
425	16.8	18.4	19.2
427	17.5	22.0	22.6
434	14.5	17.6	20.4
435	17.8	20.8	16.8
447	21.0	22.2	21.8
453	21.0	20.4	21.8
457	17.8	18.8	22.2
459	19.3	22.2	23.0
469	16.5	19.2	20.2
472	16.0	20.0	18.4
482	17.5	12.2	20.8
486	21.0	25.0	23.2
494	21.8	22.2	23.2
502	20.0	19.4	19.0

MEAN	17.8	19.6	20.9
S.D.	2.33	2.80	1.91
N	25	25	25

--: Data Unavailable

<sup>a</sup>Inclusive intervals

<sup>b</sup>Food in on day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)<sup>a</sup>

STUDY: 154

GROUP: 4-F  
DOSE: 30 (mg base/kg/day)

SEX: FEMALE

ANIMAL # DAY 10<sup>b</sup> DAY 15 DAY 20

354	16.8	15.8	16.8
356	13.5	13.6	19.0
370	17.0	14.0	18.4
374	12.8	9.6	18.6
379	11.8	10.0	14.4
382	18.0	24.2	19.0
385	9.5	8.4	17.6
392	13.8	13.4	21.2
399	16.8	16.0	20.2
404	17.5	15.6	18.4
410	12.5	17.2	22.0
417	15.3	11.8	17.6
440	14.5	9.6	15.6
441	9.3	13.0	20.8
444	13.8	10.4	15.6
448	14.8	9.4	13.0
450	15.5	8.0	13.6
455	18.0	15.8	20.0
460	13.3	9.6	16.0
475	8.8	13.6	17.2
483	13.8	15.8	20.6
490	14.8	12.0	15.0
491	15.5	13.2	14.8
492	13.5	8.0	15.8
503	14.3	10.0	15.8
MEAN	14.2	12.7	17.5
S.D.	2.54	3.70	2.50
N	25	25	25

--: Data Unavailable

<sup>a</sup> Inclusive intervals

<sup>b</sup> Food in on day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams) <sup>a</sup>

STUDY: 154

GROUP: 5-F

SEX: FEMALE

DOSE: 1000 (mg/kg/day) <sup>c</sup>

ANIMAL # DAY 10 <sup>b</sup> DAY 15 DAY 20

353	18.0	19.4	24.2
362	15.5	18.2	21.0
364	15.5	18.2	21.8
366	18.5	17.6	22.2
368	16.8	18.2	19.6
372	17.5	17.2	19.2
389	19.8	17.0	26.0
391	18.0	18.6	23.0
401	14.8	16.2	22.8
407	16.5	17.2	20.4
422	16.8	15.4	21.2
423	17.8	18.8	22.8
426	16.3	18.4	21.4
430	14.8	18.0	21.4
432	17.5	21.4	24.4
442	19.3	20.4	21.2
445	18.3	17.0	18.4
465	16.5	15.8	20.4
468	18.0	21.2	21.6
476	18.8	19.4	20.0
477	19.0	19.2	21.0
485	13.5	16.6	24.8
493	18.0	18.2	17.6
496	19.0	19.0	25.0
499	18.5	19.8	22.2

MEAN	17.3	18.3	21.7
S.D.	1.59	1.54	2.08
N	25	25	25

--: Data Unavailable

<sup>a</sup> Inclusive intervals

<sup>b</sup> Food in on day 6

<sup>c</sup> Retinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL FOOD CONSUMPTION (Grams)<sup>a</sup>

STUDY: 154

GROUP: 1-F

SEX: FEMALE

DOSE: 0 (mg base/kg/day)

ANIMAL # DAY 10<sup>b</sup> DAY 15 DAY 20

346	68	112	100
349	72	105	102
352	81	114	118
357	84	122	122
367	70	107	116
369	74	115	120
381	88	124	115
386	78	110	113
388	85	126	125
396	79	112	126
412	85	118	119
419	78	105	114
421	81	110	110
428	79	119	89
437	81	115	119
438	74	107	113
451	77	104	108
452	95	123	129
456	87	113	112
467	91	135	115
471	69	99	98
474	86	111	106
497	81	104	100
500	89	117	121
501	81	115	83

MEAN	81	114	112
S.D.	7.0	8.2	11.3
N	25	25	25

--: Data Unavailable

<sup>a</sup>Inclusive intervals

<sup>b</sup>Food in on day 6



DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL FOOD CONSUMPTION (Grams)<sup>a</sup>

STUDY: 154

GROUP: 2-F  
DOSE: 3 (mg base/kg/day)

SEX: FEMALE

ANIMAL # DAY 10<sup>b</sup> DAY 15 DAY 20

350	70	109	110
355	74	98	105
358	77	100	104
360	76	108	114
361	78	120	117
376	77	106	111
393	66	97	97
398	74	97	102
402	76	103	111
403	84	93	96
405	82	119	115
413	75	99	102
415	64	99	107
431	76	100	104
436	80	122	122
439	89	114	117
454	80	112	115
449	78	103	112
462	76	105	103
473	82	98	88
480	84	116	122
481	85	103	122
484	75	110	110
489	66	124	71
495	72	85	94

MEAN	77	106	107
S.D.	6.1	9.7	11.7
N	25	25	25

--: Data Unavailable

<sup>a</sup>Inclusive intervals

<sup>b</sup>Food in on day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL FOOD CONSUMPTION (Grams)<sup>a</sup>

STUDY: 154

GROUP: 3-F

SEX: FEMALE

DOSE: 10 (mg base/kg/day)

ANIMAL # DAY 10<sup>b</sup> DAY 15 DAY 20

351	67	98	98
371	70	102	119
378	68	85	104
380	71	114	108
383	60	70	104
384	45	103	107
390	67	93	95
395	79	105	112
400	69	108	119
420	77	90	91
424	72	82	95
425	67	92	96
427	70	110	113
434	58	88	102
435	71	104	84
447	84	111	109
453	84	102	109
457	71	94	111
459	77	111	115
469	66	96	101
472	64	100	92
482	70	61	104
486	84	125	116
494	87	111	116
502	80	97	95

MEAN	71	98	105
S.D.	9.3	14.0	9.5
N	25	25	25

--: Data Unavailable

<sup>a</sup>Inclusive intervals

<sup>b</sup>Food in on day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL FOOD CONSUMPTION (Grams) <sup>a</sup>

STUDY: 154

GROUP: 4-F

SEX: FEMALE

DOSE: 30 (mg base/kg/day)

ANIMAL # DAY 10 <sup>b</sup> DAY 15 DAY 20

354	67	79	84
356	54	68	95
370	68	70	92
374	51	48	93
379	47	50	72
382	72	121	95
385	38	42	88
392	55	67	106
399	67	80	101
404	70	78	92
410	50	86	110
417	61	59	88
440	58	48	78
441	37	65	104
444	55	52	78
448	59	47	65
450	62	40	68
455	72	79	100
460	53	48	80
475	35	68	86
483	55	79	103
490	59	60	75
491	62	66	74
492	54	40	79
503	57	50	79

MEAN	57	64	87
S.D.	10.2	18.5	12.5
N	25	25	25

--: Data Unavailable

<sup>a</sup> Inclusive intervals

<sup>b</sup> Food in on day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

DRAFT

INDIVIDUAL FOOD CONSUMPTION (Grams)<sup>a</sup>

STUDY: 154

GROUP: 5-F

SEX: FEMALE

DOSE: 1000<sup>b</sup> (mg/kg/day)<sup>c</sup>  
ANIMAL # DAY 10<sup>b</sup> DAY 15 DAY 20

353	72	97	121
362	62	91	105
364	62	91	109
366	74	88	111
368	67	91	98
372	70	86	96
389	79	85	130
391	72	93	115
401	59	81	114
407	66	86	102
422	67	77	106
423	71	94	114
426	65	92	107
430	59	90	107
432	70	107	122
442	77	102	106
445	73	85	92
465	66	79	102
468	72	106	108
476	75	97	100
477	76	96	105
485	54	83	124
493	72	91	88
496	76	95	125
499	74	99	111

MEAN	69	91	109
S.D.	6.4	7.7	10.4
N	25	25	25

--: Data Unavailable

<sup>a</sup> Inclusive intervals

<sup>b</sup> Food in on day 6

<sup>c</sup> Retinol Palmitate given on GD9 and GD10 only

DRAFT

APPENDIX 5  
Teratology Report





**Pathology Associates, Inc.**

Suite I  
15 Worman's Mill Court  
Frederick, MD 21701  
(301) 663-1644  
(301) 663-8994 FAX

---

TERATOLOGY REPORT

FOR

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

UIC/TRL STUDY NUMBER: 154

PREPARED FOR

TOXICOLOGY RESEARCH LABORATORY (TRL)  
UNIVERSITY OF ILLINOIS AT CHICAGO  
DEPARTMENT OF PHARMACOLOGY  
1940 W. TAYLOR ST.  
CHICAGO, IL 60612-7353

## TABLE OF CONTENTS

<u>Section</u>	<u>Page No.</u>
I. QUALITY ASSURANCE STATEMENT .....	4
II. MATERIALS AND METHODS .....	5
A. Cesarean Section .....	5
B. Fetal Evaluation .....	6
1. External Examination .....	6
2. Visceral Examination .....	6
3. Skeletal Examination .....	6
C. Statistical Analyses .....	6
III. RESULTS .....	7
A. Survival and Pregnancy .....	7
B. Maternal Gross Necropsy .....	8
C. Cesarean Section Data .....	8
D. Fetal Morphological Observations .....	9
IV. DISCUSSION AND CONCLUSIONS .....	9
V. REFERENCES .....	10

## INDEX OF TABLES AND APPENDICES

<u>Table</u>	<u>Page No.</u>
1. Summary of Pregnancy Status . . . . .	11
2. Summary of Gross Necropsy Observations . . . . .	12
3. Summary of Cesarean Section Data . . . . .	13
4. Summary of Fetal Observations (Absolute) - Malformations . . . . .	15
5. Summary of Fetal Observations (Absolute) - Variations . . . . .	17
6. Summary of Fetal Observations (Percent) - Malformations . . . . .	18
7. Summary of Fetal Observations (Percent) - Variations . . . . .	20
 <u>Appendix</u>	
A. Individual Maternal Gross Necropsy Observations . . . . .	21
B. Individual Cesarean Section Data . . . . .	26
C. Individual Gravid Uterus And Fetal Body Weight Data . . . . .	31
D. Individual Fetal Morphological Observations . . . . .	36



# Pathology Associates, Inc.

15 Woman's Mill Court  
Suite I  
Frederick, MD 21701  
(301) 663-1644  
(301) 663-8994 FAX

## I. QUALITY ASSURANCE STATEMENT

This teratology project has been inspected and audited by the PAI Quality Assurance Unit (QAU) as required by the Good Laboratory Practice (GLP) regulations promulgated by the U.S. Food and Drug Administration. The following table is a record of the inspections/audits performed and reported by the QAU.

<u>Date of Inspection</u>	<u>Phase Inspected</u>	<u>Date Findings Reported to Management/ Study Teratologist</u>
12/07/94	Skeletal Examination	12/07/94
12/29/94	Wilson's Soft Tissue Examination	12/29/94
03/25/95	Individual Animal Data (Raw Data)	03/28/95
03/25-28/95	Individual Animal Data (Data Entry)	03/28/95
03/27-28/95	Draft Teratology Report	03/28/95
03/29/95	Second Draft Teratology Report	03/29/95

Patricia L. Bussard  
Quality Assurance Auditor

Date

TRL Study No. 154  
DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

Developmental Toxicity (Segment II) Study of WR238605 Succinate in Rats

## II. MATERIALS AND METHODS

### A. Cesarean Section

On gestation day 20, all rats were euthanized in a random order by carbon dioxide asphyxiation. The abdominal and thoracic cavities were opened by a ventral midline incision and the uterus and ovaries removed from the body. A gross necropsy was then performed. Abnormalities were recorded and tissue samples containing lesions were preserved in 10% neutral buffered formalin for possible histopathological examination. Following the gross necropsy examination, the carcass of each dam was discarded.

The uterus was examined and weighed. For gravid females, the number of corpora lutea on each ovary was recorded and the ovaries were discarded after evaluation. The uterus was opened and the development of the fetuses was classified using the following criteria:

- Viable fetus: a term fetus which responds to stimuli.
- Nonviable fetus: a term fetus which did not respond to stimuli *in utero* or was not breathing.
- Early resorption: an implantation for which it was not grossly evident that organogenesis had occurred.
- Late resorption: an implantation for which it was grossly evident that organogenesis had occurred. A fetus with autolysis was considered a late resorption.

The number and location of fetuses, early resorption(s), late resorption(s) and their uterine position were documented using the following procedure. All implantation sites were numbered in consecutive fashion per uterine horn beginning with the left distal horn and proceeding to the cervix and then similarly for the right uterine horn beginning with the distal end and proceeding to the cervix.



## B. Fetal Evaluation

### 1. External Examination

A detailed examination of each fetus was conducted to include the eyes, palate, head shape, extremities and general body integument. The fetuses were then weighed, externally sexed, euthanized by intraperitoneal injection of a 40% sodium pentobarbital solution (approximately 0.04 ml/fetus) and tagged for unique identification.

### 2. Visceral Examination

Approximately one-half of the fetuses from each litter were preserved in Bouin's Fixative for subsequent visceral evaluation using the Wilson's soft tissue free hand slicing technique (Wilson, 1965.)

### 3. Skeletal Examination

The remaining fetuses in each litter were retained in 95% alcohol for skeletal examination. These fetuses were macerated in 1% potassium hydroxide, stained with Alizarin Red S and cleared with glycerin (Dawson, 1926). The fetuses were then examined microscopically for skeletal formation and ossification.

During processing for skeletal examination, the fetuses from a few litters in each group disarticulated. The bones from these fetuses completed the staining procedure, however, it was not possible to perform a complete skeletal examination of the fetuses. Although individual skeletal data were not collected, a general examination of the bones from each of the litters in the control and WR238605 Succinate groups treated did not reveal any gross structural abnormalities. The bones from litters in the positive control group appear to have structural defects consistent with the other intact (not disarticulated) litters from this group. This occurrence had no impact on the outcome of the study since a minimum of 20 litters was available in each group for a complete examination.

## C. Statistical Analyses

The incidences or the means and standard deviations of the maternal and fetal observations were calculated. Gravid uterus weights and fetal body weights were analyzed by a one-way analysis of variance (ANOVA). If a significant F ratio was obtained ( $p \leq 0.05$ ), Dunnett's test was used for pair-wise comparison of all treatment groups to the control group.

The numbers of preimplantation loss, early and late resorptions, nonviable fetuses, viable fetuses, post-implantation loss, total implantation sites and corpora lutea were compared across groups using the Kruskal-Wallis nonparametric ANOVA test. If a significant effect occurred ( $p \leq 0.05$ ), the Wilcoxon (Mann-Whitney U) test was used for pair-wise comparisons of each treated group to the control group.

Calculations were as follows:

$$\text{Pre-implantation loss \%} = \frac{\#Corpora\ lutea - \#Implants}{\#Corpora\ Lutea} \times 100$$

$$\text{Post-implantation loss \%} = \frac{\#Implants - \#Viable\ fetuses}{\#Implants} \times 100$$

$$\text{Total loss/litter \%} = \frac{\#Corpora\ lutea - \#Viable\ fetuses}{\#Corpora\ Lutea} \times 100$$

Male to female fetal sex ratios were compared by using the Chi-square test. The incidences of malformations and variations were compared using the Fisher's exact test with the litter as the experimental unit. The total number of litters with external, visceral and skeletal malformations as well as the total number of litters with malformations and variations were also statistically compared.

Statistical analyses of the cesarean section and fetal morphological examination data were performed using an IBM<sup>TM</sup> compatible computer with SAS computer programs (SAS/STAT User's Guide, 1989).

### III. RESULTS

#### A. Survival and Pregnancy

##### Table 1 (Summary Data)

All females survived to scheduled Cesarean section on gestation day 20. The pregnancy rate was 100% for each study group.

B. Maternal Gross Necropsy

Table 2 (Summary Data)  
Appendix A (Individual Data)

No treatment-related findings were observed in the 3 mg base/kg/day group or the positive control group. A treatment-related increase in the incidence in the number of females with enlarged spleens was observed at the 30 mg base/kg/day level as compared to the vehicle control. The incidence in the 10 mg base/kg/day group was limited to one female and was, therefore, not considered biologically meaningful. The gross lesions retained in 10% neutral buffered formalin at necropsy included spleens from 17 females and kidneys from 2 females. The lesions were not processed or examined histopathologically.

C. Cesarean Section Data

Table 3 (Summary Data)  
Appendices B and C (Individual Data)

There were no biologically meaningful differences between the vehicle control and the WR238605 Succinate treated groups in the cesarean section parameters measured, including the mean numbers of corpora lutea, implantation sites, pre-implantation loss, viable and nonviable fetuses, early and late resorptions, post-implantation loss, total loss/litter, fetal sex ratios, and gravid uterus and fetal weights. The mean number of viable fetuses in the 3 mg base/kg/day group was statistically increased. The increase was considered incidental since a similar increase was not observed in 10 or 30 mg base/kg/day groups. Treatment-related differences noted in the positive control group included statistically significant increases in the numbers of early resorptions, and post-implantation loss, the percent total loss/litter and a corresponding decrease in the mean number of viable fetuses. In addition, the gravid uterus weight and mean fetal body weights (total litter, male and female) were significantly reduced in the positive control group.



#### D. Fetal Morphological Observations

Tables 4-7 (Summary Data)  
Appendix D (Individual Data)

No statistically significant or apparent treatment-related malformations or developmental variations were observed at the 3, 10 or 30 mg base/kg/day levels. In the positive control group, statistical increases were observed in the number of litters with external and skeletal malformations. The external malformations primarily involved structures of the head including the eyes, cranium, jaws, facial papillae and pinnae. The skeletal malformations included skull anomalies, vertebral anomalies with associated rib anomaly and fused ribs. The incidences of four developmental variations, i.e. reduced ossification/unossified skull bones, 14th rudimentary ribs, 14th full ribs and 27 presacral vertebrae, were statistically increased in the positive control group.

#### IV. DISCUSSION AND CONCLUSIONS

This study was conducted to evaluate the embryo/fetal toxicity and the teratogenic potential of WR238605 Succinate in rats.

All females survived to scheduled cesarean section on gestation day 20. The pregnancy rate was 100% in each study group. An increase in the incidence of enlarged spleens was observed at necropsy for females in the 30 mg base/kg/day WR238605 Succinate treated group. Only one female in the 10 mg base/kg/day group was affected. Cesarean section data were comparable between the vehicle control and the 3, 10 and 30 mg base/kg/day groups. Similarly, no biologically meaningful differences were noted in the fetal morphological examination data from the vehicle control or WR238605 Succinate treated groups.

The use of Vitamin A (Retinol Palmitate) as a positive control agent was effective in producing a teratogenic response. A dose level of 1000 mg/kg/day, administered on gestation days 9 and 10, resulted in increased post-implantation loss and percent total loss/litter as characterized by an increase in early resorptions and a decrease in viable fetuses. In addition, gravid uterus and fetal body weights were significantly decreased while the incidences of external and skeletal malformations were significantly increased. Salient findings were primarily related to the structures of the head, vertebral column and ribs. In addition, the incidences of four developmental variations, i.e. reduced ossification/unossified skull bones, 14th rudimentary ribs, 14th full ribs and 27 presacral vertebrae, were statistically increased as compared to the vehicle control group.

Draft Report  
Study No. 154

In conclusion, maternal toxicity, expressed as enlarged spleens, occurred at the 10 and 30 mg base/kg/day levels. The effect was minimal in the 10 mg base/kg/day group. No evidence embryo/fetal toxicity or teratogenicity was produced at any level tested. The no-effect level for developmental toxicity of WR238605 Succinate in rats was established at 30 mg base/kg/day. Results of the positive control group demonstrated that the procedures utilized in the conduct of this study were sufficiently sensitive to identify potential developmental toxicants.

Date: March 28, 1995

---

Michael D. Mercieca, B.S.  
Teratologist

## V. REFERENCES

Wilson, J.G. (1965). Methods for administering drugs and detecting malformations in experimental animals. In: Teratology Principles and Techniques (Wilson, J.G. and Warkany, J., eds.). Un. Chicago Press pp 262-277.

Dawson, AB (1926). A note on the cleared specimens with Alizarin Red S. Stain Technol. 1:123-124.

SAS Institute Inc., SAS/STAT User's Guide, Version 6, Fourth Edition, Volume 2  
Cary, NC:SAS Institute Inc., 1989. 846 pp.



TABLE 1

UIC/TRL STUDY NO. 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

## SUMMARY OF PREGNANCY STATUS

GROUP: DOSE LEVEL (MG BASE/KG/DAY):	1		2		3		4		5	
	No.	%	No.	%	No.	%	No.	%	No.	%
FEMALES ON STUDY	25		25		25		25		25	
FOUND DEAD/EUTHANIZED	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
EXAMINED AT CESAREAN SECTION	25	100.0	25	100.0	25	100.0	25	100.0	25	100.0
NONGRAVID	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
GRAVID	25	100.0	25	100.0	25	100.0	25	100.0	25	100.0
WITH TOTAL RESORPTIONS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
WITH LIVE FETUSES	25	100.0	25	100.0	25	100.0	25	100.0	25	100.0
TOTAL GRAVID FEMALES	25	100.0	25	100.0	25	100.0	25	100.0	25	100.0

\*RETINOL PALMITATE (250,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10)

TABLE 2

UIC/TRL STUDY NO. 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

## SUMMARY OF GROSS NECROPSY OBSERVATIONS

	GROUP:				
	1	2	3	4	5
DOSE LEVEL (MG BASE/KG/DAY):	0	3	10	30	1000 MG/KG/DAY <sup>a</sup>
NUMBER OF FEMALES NECROPSIED ON GESTATION DAY 20	25	25	25	25	25
NO ABNORMALITIES DETECTED	25	25	24	8	24
KIDNEY(S)					
- HYDRONEPHROSIS	0	0	0	1	1
SPLEEN					
-ENLARGED	0	0	1	16	0
<sup>a</sup> RETINOL PALMITATE (250,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10)					

TABLE 3

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

## SUMMARY OF CESAREAN SECTION DATA

GROUP: LEVEL (MG BASE/KG/DAY):	1		2		3		4		5	
	25	0	25	3	25	10	25	30	25	1000 MG/KG/DAY <sup>a</sup>
NUMBER OF GRAVID FEMALES	25		25		25		25		25	
NUMBER OF CORPORA LUTEA	MEAN S.D.	13.4 1.6	13.9 1.4		13.8 1.8		13.1 <sup>b</sup> 2.5		14.7 2.3	
NUMBER OF IMPLANTATIONS	MEAN S.D.	12.6 1.9	13.5 1.2		13.3 1.5		12.2 3.1		13.0 1.9	
PRE-IMPLANTATION LOSS <sup>c</sup>	MEAN S.D.	0.8 (5.5%) 1.5	0.4 (2.7%) <sup>b</sup> 0.8		0.5 (3.0%) 1.2		1.0 (8.6%) 1.8		1.7 (10.7%) 2.2	
NUMBER OF VIABLE FETUSES	MEAN S.D.	12.1 1.6	13.0* 1.5		12.6 1.5		11.5 3.3		10.7* 2.4	
NUMBER OF NONVIABLE FETUSES	MEAN S.D.	0.0 0.0	0.0 0.0		0.0 0.0		0.0 0.0		0.0 0.0	
NUMBER OF EARLY RESORPTIONS	MEAN S.D.	0.5 0.8	0.5 0.8		0.7 0.9		0.7 1.0		2.1* 2.3	
NUMBER OF LATE RESORPTIONS	MEAN S.D.	0.1 0.3	0.0 0.2		0.0 0.0		0.0 0.2		0.1 0.3	
POST-IMPLANTATION LOSS <sup>c</sup>	MEAN S.D.	0.6 (3.9%) 0.9	0.5 (3.9%) 0.8		0.7 (5.0%) 0.9		0.7 (6.4%) 1.0		2.2 (16.6%)* 2.3	
TOTAL LOSS/LITTER (%)	MEAN S.D.	9.3 11.3	6.2 7.4		7.9 8.2		14.5 19.3		25.8* 17.8	

<sup>a</sup>RETINOL PALMITATE (250,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10)<sup>b</sup>DOES NOT INCLUDE ONE FEMALE FOR WHICH CORPORA LUTEA WERE NOT RECORDED<sup>c</sup>THE MEAN PERCENTAGES OF PRE-IMPLANTATION LOSS AND POST-IMPLANTATION LOSS ARE INCLUDED NEXT TO THE RESPECTIVE MEANS IN PARENTHESES  
SIGNIFICANTLY DIFFERENT FROM CONTROL: \* = P<0.05

TABLE 3 (CONT.)

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

## SUMMARY OF CESAREAN SECTION DATA

GROUP:		1		2		3		4		5	
LEVEL (MG BASE/KG/DAY):		0		3		10		30		1000 MG/KG/DAY <sup>a</sup>	
SEX: MALES / FEMALES	MEAN	5.9 6.2		6.6 6.4		6.5 6.1		5.8 5.8		5.2 5.5	
	S.D.	2.4 2.4		1.9 2.0		2.1 1.9		2.3 2.3		1.9 2.5	
FETAL WEIGHT (g) (LITTER) <sup>b</sup>	MEAN	3.70		3.76		3.80		3.57		3.22*	
	S.D.	0.28		0.25		0.23		0.30		0.36	
(MALES) <sup>b</sup>	MEAN	3.75		3.83		3.87		3.68		3.32*	
	S.D.	0.32		0.26		0.25		0.29		0.37	
(FEMALES) <sup>b</sup>	MEAN	3.64		3.68		3.70		3.49		3.13*	
	S.D.	0.26		0.24		0.23		0.29		0.40	
GRAVID UTERUS WEIGHT (g)	MEAN	68.66		74.00		72.61		63.47		58.46*	
	S.D.	8.11		7.79		8.29		17.48		13.59	

<sup>a</sup>RETINOL PALMITATE (250,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10)<sup>b</sup>VALUES FOR EACH GROUP REPRESENTS THE MEAN OF THE TOTAL OF THE LITTER MEANS SIGNIFICANTLY DIFFERENT FROM CONTROL: \* = P<0.05

TABLE 4

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 IN RATS

SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS  
- ABSOLUTE -

GROUP:	FETUSES						LITTERS					
	1	2	3	4	5		1	2	3	4	5	
DOSE LEVEL (MG BASE/KG/DAY):	0	3	10	30	1000	MG/KG/DAY <sup>a</sup>	25	25	10	30	1000	MG/KG/DAY <sup>a</sup>
NUMBER EXAMINED EXTERNALLY	302	325	314	288	268		25	25	25	25	25	
CEPHALOCELE	0	0	0	0	4		0	0	0	0	4*	
CLEFT PALATE	1	0	0	0	58		1	0	0	0	17*	
ANAL ATRESIA	0	0	0	0	6		0	0	0	0	2*	
ANAL OPENING SMALL IN SIZE	1	0	0	1	1		1	0	0	1	1	
MICROCEPHALY	1	0	0	0	1		1	0	0	0	1	
ENCEPHALOCELE	0	0	0	0	21		0	0	0	0	12*	
EXENCEPHALY	1	0	0	0	54		0	0	0	0	16*	
MACROSTOMIA	0	0	0	0	67		0	0	0	0	18*	
MICROSTOMIA	0	0	0	1	29		0	0	0	1	8*	
MOUTH - FLESHY PROTUBERANCES	0	0	0	0	8		0	0	0	0	3	
AGNATHIA	0	0	0	1	0		0	0	0	1	0	
MANDIBLE - MICROGNATHIA	1	0	0	0	13		1	0	0	0	8*	
MAXILLAE - MICROGNATHIA	1	0	0	0	50		1	0	0	0	18*	
MANDIBLE - MALFORMED	0	0	0	0	1		0	0	0	0	1	
MANDIBLE - CLEFTS	0	0	0	0	1		0	0	0	0	1	
FACIAL APLASIA	1	0	0	0	0		1	0	0	0	0	
VERTEBRAL DEFECT	0	0	0	0	1		0	0	0	0	1	
SPINA BIFIDA	0	0	0	0	3		0	0	0	0	2	
TONGUE - MALFORMED	0	0	0	0	1		0	0	0	0	1	
DOMED - HEAD	0	0	0	0	45		0	0	0	0	13*	
MACROPHTHALMIA	0	0	0	0	14		0	0	0	0	5*	
OPEN EYELID(S)	0	0	0	0	68		0	0	0	0	18*	
MACROGLOSSIA	0	0	0	0	61		0	0	0	0	15*	
PINNA ANOMALY	0	0	0	0	198		0	0	0	0	24*	
FACIAL PAPILLA ANOMALY	0	0	0	1	256		0	0	0	1	25*	
TAIL ANOMALY	1	0	0	1	9		1	0	0	1	2	
MICROPHTHALMIA AND/OR ANOPHTHALMIA	0	0	0	0	79		1	0	0	1	21*	

<sup>a</sup>RETINOL PALMITATE (250,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10)

SIGNIFICANTLY DIFFERENT FROM CONTROL: \* = P&lt;0.05

NOTE: THE NUMBER OF FETUSES EXAMINED IN GROUP 3 DOES NOT INCLUDE ONE FETUS FOR WHICH AN EXTERNAL OBSERVATION WAS NOT RECORDED.



TABLE 4

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 IN RATS

## SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS

- ABSOLUTE -

GROUP:	FETUSES			LITTERS								
	1	2	3	4	5	6	7	8	9	10	11	12
DOSE LEVEL (MG BASE/KG/DAY):	0	3	10	30	1000	MG/KG/DAY <sup>a</sup>	0	3	10	30	1000	MG/KG/DAY <sup>a</sup>
NUMBER EXAMINED VISCERALLY <sup>b</sup>	149	155	159	145	132		25	24	25	25	25	25
RIGHT-SIDED AORTIC ARCH	0	0	0	0	1		0	0	0	0	0	1
HYDROCEPHALY - INTERNAL	0	0	0	0	3		0	0	0	0	0	2
BRAIN - HEMORRHAGE	1	0	0	0	0		1	0	0	0	0	0
MENINGOCELE	0	0	0	0	2		0	0	0	0	0	2
NUMBER EXAMINED SKELETALLY <sup>c</sup>	134	135	137	118	108		22	21	22	21	20	
VERTEBRAL ANOMALY WITH ASSOCIATED RIB ANOMALY	0	1	0	0	25		0	1	0	0	14*	
FUSED RIBS	0	0	0	0	5		0	0	0	0	5*	
SKULL ANOMALY	0	0	0	0	40		0	0	0	0	14*	
TOTAL MALFORMATIONS	4	0	0	2	266		4	0	0	2	25*	
NUMBER WITH EXTERNAL MALFORMATIONS	1	0	0	0	5		1	0	0	0	3	
NUMBER WITH VISCERAL MALFORMATIONS	0	1	0	0	56		0	1	0	0	17*	
TOTAL WITH MALFORMATIONS	4	1	0	2	267		4	1	0	2	25*	

<sup>a</sup>RETINOL PALMITATE (250,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10)<sup>b</sup>DOES NOT INCLUDE THE FETUSES FROM DAM 405 FOR WHICH VISCERAL OBSERVATIONS WERE NOT RECORDED<sup>c</sup>DOES NOT INCLUDE FETUSES FROM LITTERS WHICH WERE DISARTICULATED

SIGNIFICANTLY DIFFERENT FROM CONTROL: \* = P&lt;0.05

TABLE 5

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 IN RATS

SUMMARY OF FETAL OBSERVATIONS - VARIATIONS  
- ABSOLUTE -

GROUP:	FETUSES			LITTERS							
	1	2	3	4	5		1	2	3	4	5
DOSE LEVEL (MG BASE/KG/DAY):	0	3	10	30	1000	MG/KG/DAY <sup>a</sup>	0	3	10	30	1000
MG/KG/DAY <sup>a</sup>											
NUMBER EXAMINED EXTERNALLY	302	325	314	288	268		25	25	25	25	25
HEMATOMA	0	0	1	2	7		0	0	1	2	5
PALLID	0	2	0	0	0		0	2	0	0	0
NUMBER EXAMINED VISCERALLY <sup>b</sup>	149	155	159	145	132		25	24	25	25	25
HYDRONEPHROSIS	4	4	6	9	23		2	1	2	7	10
HYDROURETER/DISTENDED URETER	1	0	1	3	12		1	0	1	2	6
NUMBER EXAMINED SKELETALLY <sup>c</sup>	134	135	137	118	108		22	21	22	21	20
HYOID UNOSSIFIED	9	3	7	1	2		6	3	5	1	2
REDUCED OSSIFICATION/UNOSSIFIED											
SKULL BONES	11	1	12	2	84		8	1	7	2	20*
BENT RIBS	5	3	8	0	1		4	3	5	0	1
7TH CERVICAL RIBS	0	0	1	0	2		0	0	1	0	2
14TH FULL RIBS	0	0	0	0	17		0	0	0	0	9*
14TH RUDIMENTARY RIBS	0	2	1	0	45		0	2	1	0	18*
13TH RUDIMENTARY RIBS	1	0	3	4	0		1	0	2	3	0
13TH RIBS REDUCED IN OSSIFICATION	0	0	5	0	1		0	0	2	0	1
TARSALS UNOSSIFIED	2	0	0	0	0		1	0	0	0	0
PUBIS UNOSSIFIED	1	0	0	1	1		1	0	0	1	1
REDUCED OSSIFICATION OF THE VERTEBRAL											
ARCHES	1	0	0	1	2		1	0	0	1	2
STERNEBRA (E) #1 - #4 UNOSSIFIED	5	1	1	2	2		3	1	1	2	2
STERNEBRA (E) #5 - #6 UNOSSIFIED	17	24	33	23	28		10	11	16	12	12
STERNEBRA (E) MALALIGNED	39	41	42	53	60		19	19	17	19	19
25 PRESACRAL VERTEBRAE	0	0	4	0	0		0	0	3	0	0
27 PRESACRAL VERTEBRAE	0	0	0	0	92		0	0	0	0	20*
CENTRA - BIPARTITE	0	0	0	0	1		0	0	0	0	1
TOTAL WITH VARIATIONS	63	61	85	79	132		21	21	22	22	22

<sup>a</sup>RETINOL PALMITATE (250,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10)<sup>b</sup>DOES NOT INCLUDE THE FETUSES FROM DAM 405 FOR WHICH VISCERAL OBSERVATIONS WERE NOT RECORDED<sup>c</sup>DOES NOT INCLUDE FETUSES FROM LITTERS WHICH WERE DISARTICULATED

SIGNIFICANTLY DIFFERENT FROM CONTROL: \* = P&lt;0.05

NOTE: THE NUMBER OF FETUSES EXAMINED IN GROUP 3 DOES NOT INCLUDE ONE FETUS FOR WHICH

AN EXTERNAL OBSERVATION WAS NOT RECORDED.

TABLE 6

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 IN RATS

## SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS

- PERCENT -

GROUP:	FETUSES					LITTERS				
	1	2	3	4	5	1	2	3	4	5
DOSE LEVEL (MG BASE/KG/DAY):	0	3	10	30	1000	MG/KG/DAY <sup>a</sup>	0	3	10	25
NUMBER EXAMINED EXTERNALLY	302	325	314	288	268		25	25	25	25
CEPHALOCELE	0.0	0.0	0.0	0.0	1.5		0.0	0.0	0.0	16.0
CLEFT PALATE	0.3	0.0	0.0	0.0	21.6		4.0	0.0	0.0	68.0
ANAL ATRESIA	0.0	0.0	0.0	0.0	2.2		0.0	0.0	0.0	8.0
ANAL OPENING SMALL IN SIZE	0.3	0.0	0.0	0.3	0.4		4.0	0.0	0.0	4.0
MICROCEPHALY	0.3	0.0	0.0	0.0	0.4		4.0	0.0	0.0	4.0
ENCEPHALOCELE	0.0	0.0	0.0	0.0	7.8		0.0	0.0	0.0	48.0
EXENCEPHALY	0.3	0.0	0.0	0.0	20.1		0.0	0.0	0.0	64.0
MACROSTOMIA	0.0	0.0	0.0	0.0	25.0		0.0	0.0	0.0	72.0
MICROSTOMIA	0.0	0.0	0.0	0.3	10.8		0.0	0.0	0.0	32.0
MOUTH - FLESHY PROTUBERANCES	0.0	0.0	0.0	0.0	3.0		0.0	0.0	0.0	12.0
AGNATHIA	0.0	0.0	0.0	0.3	0.0		0.0	0.0	0.0	0.0
MANDIBLE - MICROGNATHIA	0.3	0.0	0.0	0.0	4.9		4.0	0.0	0.0	32.0
MAXILLAE - MICROGNATHIA	0.3	0.0	0.0	0.0	18.7		4.0	0.0	0.0	72.0
MANDIBLE - MALFORMED	0.0	0.0	0.0	0.0	0.4		0.0	0.0	0.0	4.0
MANDIBLE - CLEFTS	0.0	0.0	0.0	0.0	0.4		0.0	0.0	0.0	4.0
FACIAL APLASIA	0.3	0.0	0.0	0.0	0.0		4.0	0.0	0.0	0.0
VERTEBRAL DEFECT	0.0	0.0	0.0	0.0	0.4		0.0	0.0	0.0	4.0
SPINA BIFIDA	0.0	0.0	0.0	0.0	1.1		0.0	0.0	0.0	8.0
TONGUE - MALFORMED	0.0	0.0	0.0	0.0	0.4		0.0	0.0	0.0	4.0
DOMED - HEAD	0.0	0.0	0.0	0.0	16.8		0.0	0.0	0.0	42.0
MACROPHthalmIA	0.0	0.0	0.0	0.0	5.2		0.0	0.0	0.0	20.0
OPEN EYELID(S)	0.0	0.0	0.0	0.0	25.4		0.0	0.0	0.0	72.0
MACROGLOSSIA	0.0	0.0	0.0	0.0	22.8		0.0	0.0	0.0	60.0
PINNA ANOMALY	0.0	0.0	0.0	0.0	73.9		0.0	0.0	0.0	96.0
FACIAL PAPILLA ANOMALY	0.0	0.0	0.0	0.3	95.5		0.0	0.0	0.0	100.0
TAIL ANOMALY	0.3	0.0	0.0	0.3	3.4		4.0	0.0	0.0	8.0
MICROPHthalmIA AND/OR ANOPHTHALMIA	0.0	0.0	0.0	0.0	29.5		0.0	0.0	0.0	48.0

<sup>a</sup>RETINOL PALMITATE (250,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10)

NOTE: THE NUMBER OF FETUSES EXAMINED IN GROUP 3 DOES NOT INCLUDE ONE FETUS FOR WHICH AN EXTERNAL OBSERVATION WAS NOT RECORDED.



TABLE 6

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 IN RATS  
SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS

GROUP: DOSE LEVEL (MG BASE/KG/DAY):	- PERCENT -										LITTERS									
	FETUSES					MG/KG/DAY <sup>a</sup>					LITTERS					MG/KG/DAY <sup>a</sup>				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
NUMBER EXAMINED VISCERALLY <sup>b</sup>	149	155	159	145	132	25	24	25	25	25	25	24	25	25	25	0.0	0.0	0.0	0.0	0.0
RIGHT-SIDED AORTIC ARCH	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.0	0.0	4.0	0.0	0.0	0.0	0.0	4.0
HYDROCEPHALY - INTERNAL	0.0	0.0	0.0	0.0	2.3	0.0	0.0	0.0	0.0	2.3	0.0	0.0	0.0	0.0	8.0	0.0	0.0	0.0	0.0	8.0
BRAIN - HEMORRHAGE	0.7	0.0	0.0	0.0	0.0	4.0	0.0	0.0	0.0	0.0	4.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MENINGOCELE	0.0	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0	8.0	0.0	0.0	0.0	0.0	8.0
NUMBER EXAMINED SKELETALLY <sup>c</sup>	134	135	137	118	108	22	21	22	21	20	22	21	22	21	20	0.0	4.8	0.0	0.0	70.0
VERTEBRAL ANOMALY WITH ASSOCIATED	0.0	0.7	0.0	0.0	23.1	0.0	0.0	0.0	0.0	23.1	0.0	4.8	0.0	0.0	70.0	0.0	0.0	0.0	0.0	25.0
RIB ANOMALY	0.0	0.0	0.0	0.0	4.6	0.0	0.0	0.0	0.0	4.6	0.0	0.0	0.0	0.0	70.0	0.0	0.0	0.0	0.0	25.0
FUSED RIBS	0.0	0.0	0.0	0.0	40.7	0.0	0.0	0.0	0.0	40.7	0.0	0.0	0.0	0.0	70.0	0.0	0.0	0.0	0.0	70.0
SKULL ANOMALY	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TOTAL MALFORMATIONS	1.3	0.0	0.0	0.7	99.3	16.0	0.0	0.0	0.7	99.3	16.0	0.0	0.0	8.0	100.0	4.0	0.0	0.0	0.0	12.0
NUMBER WITH EXTERNAL MALFORMATIONS	0.7	0.0	0.0	0.0	4.6	4.0	0.0	0.0	0.0	4.6	4.0	0.0	0.0	0.0	12.0	0.0	0.0	0.0	0.0	85.0
NUMBER WITH VISCERAL MALFORMATIONS	0.0	0.7	0.0	0.0	48.3	0.0	0.0	0.0	0.0	48.3	0.0	4.8	0.0	0.1	85.0	0.0	0.0	0.0	0.1	85.0
NUMBER WITH SKELETAL MALFORMATIONS	1.3	0.3	0.0	0.7	99.6	16.0	4.0	0.0	0.7	99.6	16.0	4.0	0.0	8.0	100.0	4.0	0.0	0.0	8.0	100.0

<sup>a</sup>RETINOL PALMITATE (250,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10)

<sup>b</sup>DOES NOT INCLUDE THE FETUSES FROM DAM 405 FOR WHICH VISCERAL OBSERVATIONS WERE NOT RECORDED

<sup>c</sup>DOES NOT INCLUDE FETUSES FROM LITTERS WHICH WERE DISARTICULATED

TABLE 7

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 IN RATS

SUMMARY OF FETAL OBSERVATIONS - VARIATIONS  
- PERCENT -

GROUP:	FETUSES			LITTERS			1000 MG/KG/DAY <sup>a</sup>			1000 MG/KG/DAY <sup>a</sup>		
	1	2	3	1	2	3	1	2	3	1	2	3
DOSE LEVEL (MG BASE/KG/DAY):	0	3	10	0	3	10	0	3	10	0	3	10
NUMBER EXAMINED EXTERNALLY	302	325	314	288	268	25	25	25	25	25	25	25
HEMATOMA	0.0	0.0	0.3	0.7	2.6	0.0	0.0	0.0	4.0	0.0	8.0	20.0
PALLID	0.0	0.3	0.0	0.0	0.0	0.0	0.0	4.0	0.0	0.0	0.0	0.0
NUMBER EXAMINED VISCERALLY <sup>b</sup>	149	155	159	145	132	25	25	24	25	25	25	25
HYDRONEPHROSIS	2.7	2.6	3.8	6.2	17.4	8.0	8.0	4.2	8.0	28.0	40.0	40.0
HYDROURETER/DISTENDED URETER	0.7	0.0	0.6	2.1	9.1	4.0	4.0	0.0	4.0	8.0	24.0	24.0
NUMBER EXAMINED SKELETALLY <sup>c</sup>	134	135	137	118	108	22	22	21	22	21	20	20
HYOID UNOSSIFIED	6.7	2.2	5.1	0.8	1.9	27.3	27.3	14.3	22.7	4.8	10.0	10.0
REDUCED OSSIFICATION/UNOSSIFIED												
SKULL BONES												
BENT RIBS	8.2	0.7	8.8	1.7	77.8	36.4	36.4	4.8	31.8	9.5	100.0	100.0
7TH CERVICAL RIBS	3.7	2.2	5.8	0.0	0.9	18.2	18.2	14.3	23.8	0.0	5.0	5.0
14TH FULL RIBS	0.0	0.0	0.7	0.0	1.9	0.0	0.0	0.0	4.5	0.0	10.0	10.0
14TH RUDIMENTARY RIBS	0.0	0.0	0.0	0.0	15.7	0.0	0.0	0.0	0.0	0.0	45.0	45.0
13TH RUDIMENTARY RIBS	0.0	1.5	0.7	0.0	41.7	0.0	0.0	9.5	4.5	0.0	90.0	90.0
13TH RIBS REDUCED IN OSSIFICATION	0.7	0.0	2.2	3.4	0.0	4.5	4.5	0.0	9.1	14.3	0.0	0.0
TARSALS UNOSSIFIED	0.0	0.0	3.6	0.0	0.9	0.0	0.0	0.0	9.1	0.0	5.0	5.0
PUBIS UNOSSIFIED	1.5	0.0	0.0	0.0	0.0	4.5	4.5	0.0	0.0	0.0	0.0	0.0
REDUCED OSSIFICATION OF THE VERTEBRAL	0.7	0.0	0.0	0.8	0.9	4.5	4.5	0.0	0.0	4.8	5.0	5.0
ARCHES												
STERNEBRA (E) #1 - #4 UNOSSIFIED	0.7	0.0	0.0	0.8	1.9	4.5	4.5	0.0	0.0	4.8	10.0	10.0
STERNEBRA (E) #5 - #6 UNOSSIFIED	3.7	0.7	0.7	1.7	1.9	13.6	13.6	4.8	4.5	9.5	10.0	10.0
STERNEBRA (E) MALALIGNED	12.7	17.7	24.1	19.5	25.9	45.4	45.4	52.4	72.7	57.1	60.0	60.0
25 PRESACRAL VERTEBRAE	29.1	30.4	30.6	44.9	55.6	86.4	86.4	90.5	77.3	90.5	95.0	95.0
27 PRESACRAL VERTEBRAE	0.0	0.0	2.9	0.0	0.0	0.0	0.0	0.0	13.6	0.0	0.0	0.0
CENTRA - BIPARTITE	0.0	0.0	0.0	0.0	85.2	0.0	0.0	0.0	0.0	0.0	100.0	100.0
TOTAL WITH VARIATIONS	20.9	18.8	27.0	27.4	49.3	84.0	84.0	84.0	88.0	88.0	88.0	88.0

<sup>a</sup>RETINOL PALMITATE (250,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10)<sup>b</sup>DOES NOT INCLUDE THE FETUSES FROM DAM 405 FOR WHICH VISCERAL OBSERVATIONS WERE NOT RECORDED<sup>c</sup>DOES NOT INCLUDE FETUSES FROM LITTERS WHICH WERE DISARTICULATED

NOTE: THE NUMBER OF FETUSES EXAMINED IN GROUP 3 DOES NOT INCLUDE ONE FETUS FOR WHICH AN EXTERNAL OBSERVATION WAS NOT RECORDED.



# APPENDIX A

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

DAM#	ORGAN	OBSERVATION
346		NO ABNORMALITIES DETECTED
349		NO ABNORMALITIES DETECTED
352		NO ABNORMALITIES DETECTED
357		NO ABNORMALITIES DETECTED
367		NO ABNORMALITIES DETECTED
369		NO ABNORMALITIES DETECTED
381		NO ABNORMALITIES DETECTED
386		NO ABNORMALITIES DETECTED
388		NO ABNORMALITIES DETECTED
396		NO ABNORMALITIES DETECTED
412		NO ABNORMALITIES DETECTED
419		NO ABNORMALITIES DETECTED
421		NO ABNORMALITIES DETECTED
428		NO ABNORMALITIES DETECTED
437		NO ABNORMALITIES DETECTED
438		NO ABNORMALITIES DETECTED
451		NO ABNORMALITIES DETECTED
452		NO ABNORMALITIES DETECTED
456		NO ABNORMALITIES DETECTED
467		NO ABNORMALITIES DETECTED
471		NO ABNORMALITIES DETECTED
474		NO ABNORMALITIES DETECTED
497		NO ABNORMALITIES DETECTED
500		NO ABNORMALITIES DETECTED
501		NO ABNORMALITIES DETECTED

# APPENDIX A

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

DAM#	ORGAN	OBSERVATION
350		NO ABNORMALITIES DETECTED
355		NO ABNORMALITIES DETECTED
358		NO ABNORMALITIES DETECTED
360		NO ABNORMALITIES DETECTED
361		NO ABNORMALITIES DETECTED
376		NO ABNORMALITIES DETECTED
393		NO ABNORMALITIES DETECTED
398		NO ABNORMALITIES DETECTED
402		NO ABNORMALITIES DETECTED
403		NO ABNORMALITIES DETECTED
405		NO ABNORMALITIES DETECTED
413		NO ABNORMALITIES DETECTED
415		NO ABNORMALITIES DETECTED
431		NO ABNORMALITIES DETECTED
436		NO ABNORMALITIES DETECTED
439		NO ABNORMALITIES DETECTED
449		NO ABNORMALITIES DETECTED
454		NO ABNORMALITIES DETECTED
462		NO ABNORMALITIES DETECTED
473		NO ABNORMALITIES DETECTED
480		NO ABNORMALITIES DETECTED
481		NO ABNORMALITIES DETECTED
484		NO ABNORMALITIES DETECTED
489		NO ABNORMALITIES DETECTED
495		NO ABNORMALITIES DETECTED

# APPENDIX A

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 3: 10 MG BASE/KG/DAY

DAM#	ORGAN	OBSERVATION
351		NO ABNORMALITIES DETECTED
371		NO ABNORMALITIES DETECTED
378		NO ABNORMALITIES DETECTED
380		NO ABNORMALITIES DETECTED
383		NO ABNORMALITIES DETECTED
384		NO ABNORMALITIES DETECTED
390		NO ABNORMALITIES DETECTED
395		ENLARGED
400	SPLEEN	NO ABNORMALITIES DETECTED
420		NO ABNORMALITIES DETECTED
424		NO ABNORMALITIES DETECTED
425		NO ABNORMALITIES DETECTED
427		NO ABNORMALITIES DETECTED
434		NO ABNORMALITIES DETECTED
435		NO ABNORMALITIES DETECTED
447		NO ABNORMALITIES DETECTED
453		NO ABNORMALITIES DETECTED
457		NO ABNORMALITIES DETECTED
459		NO ABNORMALITIES DETECTED
469		NO ABNORMALITIES DETECTED
472		NO ABNORMALITIES DETECTED
482		NO ABNORMALITIES DETECTED
486		NO ABNORMALITIES DETECTED
494		NO ABNORMALITIES DETECTED
502		NO ABNORMALITIES DETECTED

# APPENDIX A

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 4: 30 MG BASE/KG/DAY

DAM#	ORGAN	OBSERVATION
354	SPLEEN	ENLARGED
356	SPLEEN	ENLARGED
370	SPLEEN	ENLARGED
374		NO ABNORMALITIES DETECTED
379		NO ABNORMALITIES DETECTED
382		NO ABNORMALITIES DETECTED
385	KIDNEYS	HYDRONEPHROSIS (BILATERAL)
392	SPLEEN	ENLARGED
399	SPLEEN	ENLARGED
404		NO ABNORMALITIES DETECTED
410	SPLEEN	ENLARGED
417		NO ABNORMALITIES DETECTED
440		NO ABNORMALITIES DETECTED
441	SPLEEN	ENLARGED
444	SPLEEN	ENLARGED
448	SPLEEN	ENLARGED
450	SPLEEN	ENLARGED
455	SPLEEN	ENLARGED
460	SPLEEN	ENLARGED
475	SPLEEN	ENLARGED
483	SPLEEN	ENLARGED
490		NO ABNORMALITIES DETECTED
491	SPLEEN	ENLARGED
492	SPLEEN	ENLARGED
503		NO ABNORMALITIES DETECTED



# APPENDIX A

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

DAM#	ORGAN	OBSERVATION
353		NO ABNORMALITIES DETECTED
362		NO ABNORMALITIES DETECTED
364		NO ABNORMALITIES DETECTED
366		NO ABNORMALITIES DETECTED
368		NO ABNORMALITIES DETECTED
372		NO ABNORMALITIES DETECTED
389		NO ABNORMALITIES DETECTED
391		NO ABNORMALITIES DETECTED
401		NO ABNORMALITIES DETECTED
407		NO ABNORMALITIES DETECTED
422		NO ABNORMALITIES DETECTED
423		NO ABNORMALITIES DETECTED
426		HYDRONEPHROSIS (RIGHT)
430	KIDNEY	NO ABNORMALITIES DETECTED
432		NO ABNORMALITIES DETECTED
442		NO ABNORMALITIES DETECTED
445		NO ABNORMALITIES DETECTED
465		NO ABNORMALITIES DETECTED
468		NO ABNORMALITIES DETECTED
476		NO ABNORMALITIES DETECTED
477		NO ABNORMALITIES DETECTED
485		NO ABNORMALITIES DETECTED
493		NO ABNORMALITIES DETECTED
496		NO ABNORMALITIES DETECTED
499		NO ABNORMALITIES DETECTED

# APPENDIX B

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS  
INDIVIDUAL CESAREAN SECTION DATA

GROUP 1: 0 MG/KG/DAY

DAM#	CORPORA LUTEA		IMPLANTATIONS		SEX		VIABLE FETUSES		NONVIABLE FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS	
	TOTAL		TOTAL		TOTAL		TOTAL		TOTAL		TOTAL		TOTAL	
	LEFT	RIGHT	LEFT	RIGHT	M	F	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT
346	6	7	13	6	7	5	5	7	12	0	0	0	0	0
349	8	8	16	3	4	6	3	7	10	0	0	0	0	0
352	7	8	15	6	8	5	6	7	13	0	0	0	0	0
357	6	9	15	6	6	8	6	8	14	0	0	1	0	0
367	6	5	11	6	6	1	6	1	7	0	0	0	0	0
369	5	7	12	5	2	9	4	7	11	0	0	0	0	1
381	5	8	13	5	3	10	5	8	13	0	0	0	0	0
386	6	7	13	4	7	4	4	7	11	0	0	0	0	0
388	8	7	15	8	4	9	7	6	13	0	0	1	0	0
396	5	8	13	5	8	5	5	8	13	0	0	0	0	0
412	6	7	13	6	3	9	6	6	12	0	0	0	0	0
419	8	8	16	7	4	7	6	5	11	0	0	1	2	0
421	6	7	13	6	5	8	6	7	13	0	0	0	0	0
428	7	5	12	7	5	7	7	5	12	0	0	0	0	0
437	6	7	13	6	4	9	6	7	13	0	0	0	0	0
438	5	7	12	5	7	5	5	7	12	0	0	0	0	0
451	4	9	13	4	5	8	4	9	13	0	0	0	0	0
452	8	7	15	8	12	3	8	7	15	0	0	0	0	0
456	4	9	13	4	6	6	3	9	12	0	0	1	0	0
467	7	9	16	7	9	4	6	7	13	0	0	1	2	1
471	4	7	11	4	6	5	4	7	11	0	0	0	0	0
474	7	8	15	7	5	8	6	7	13	0	0	1	2	0
497	6	6	12	6	6	5	6	5	11	0	0	0	0	0
500	7	7	14	7	11	2	7	6	13	0	0	1	1	0
501	4	7	11	4	5	6	4	7	11	0	0	0	0	0
TOTAL	335		316	148	154			302		0		12		2
MEAN	13.4		12.6	5.9	6.2			12.1		0.0		0.5		0.1
S.D.	1.6		1.9	2.4	2.4			1.6		0.0		0.8		0.3
N	25		25	25	25			25		25		25		25

# APPENDIX B

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL CESAREAN SECTION DATA

GROUP 3: 10 MG BASE/KG/DAY

DAM#	CORPORA LUTEA				IMPLANTATIONS				SEX		VIABLE FETUSES				NONVIABLE FETUSES				EARLY RESORPTIONS				LATE RESORPTIONS			
	LEFT		RIGHT		LEFT		RIGHT		M	F	LEFT		RIGHT		LEFT		RIGHT		LEFT		RIGHT		LEFT		RIGHT	
	TOTAL	9	2	11	TOTAL	9	2	11			TOTAL	9	2	11	TOTAL	9	2	11	TOTAL	9	2	11	TOTAL	9	2	11
351	9	2	11	11	11	9	2	11	5	6	9	2	11	0	0	0	0	0	0	0	0	0	0	0	0	0
371	7	8	15	14	14	5	9	14	7	7	5	9	14	0	0	0	0	0	0	0	0	0	0	0	0	0
378	10	6	16	13	13	8	5	13	7	6	8	5	13	0	0	0	0	0	0	0	0	0	0	0	0	0
380	7	7	14	14	14	7	7	14	8	5	7	6	13	0	0	0	0	1	1	1	1	0	0	0	0	0
383	7	5	12	11	11	6	5	11	1	9	6	4	10	0	0	0	0	1	1	1	1	0	0	0	0	0
384	6	9	15	14	14	6	8	14	10	4	6	8	14	0	0	0	0	0	0	0	0	0	0	0	0	0
390	8	5	13	13	13	8	5	13	7	6	8	5	13	0	0	0	0	0	0	0	0	0	0	0	0	0
395	3	10	13	13	13	3	10	13	8	4	3	9	12	0	0	0	0	1	1	1	1	0	0	0	0	0
400	10	8	18	13	13	10	3	13	3	10	10	3	13	0	0	0	0	0	0	0	0	0	0	0	0	0
420	7	8	15	15	15	7	8	15	8	7	7	8	15	0	0	0	0	0	0	0	0	0	0	0	0	0
424	9	5	14	14	14	9	5	14	4	10	9	5	14	0	0	0	0	0	0	0	0	0	0	0	0	0
425	3	11	14	13	13	2	11	13	6	6	2	10	12	0	0	0	0	1	1	1	1	0	0	0	0	0
427	6	8	14	14	14	6	8	14	7	6	5	8	13	0	0	0	0	1	1	1	1	0	0	0	0	0
434	6	9	15	15	15	6	9	15	5	9	6	8	14	0	0	0	0	0	0	0	0	0	0	0	0	0
435	7	6	13	13	13	7	6	13	6	3	5	5	10	0	0	0	0	2	1	1	1	0	0	0	0	0
447	6	7	13	13	13	6	7	13	7	6	6	7	13	0	0	0	0	0	0	0	0	0	0	0	0	0
453	8	8	16	16	16	8	8	16	7	7	6	8	14	0	0	0	0	2	2	2	2	0	0	0	0	0
457	4	9	13	13	13	4	9	13	8	4	4	8	12	0	0	0	0	0	1	1	1	0	0	0	0	0
459	5	11	16	16	16	5	11	16	8	7	4	11	15	0	0	0	0	1	1	1	1	0	0	0	0	0
469	4	7	11	11	11	4	7	11	6	5	4	7	11	0	0	0	0	0	0	0	0	0	0	0	0	0
472	9	5	14	14	14	9	5	14	11	3	9	5	14	0	0	0	0	0	0	0	0	0	0	0	0	0
482	8	4	12	12	12	8	4	12	6	6	8	4	12	0	0	0	0	0	0	0	0	0	0	0	0	0
486	9	6	15	15	15	9	6	15	7	5	8	4	12	0	0	0	0	1	2	3	3	0	0	0	0	0
494	7	4	11	11	11	7	4	11	5	6	7	4	11	0	0	0	0	0	0	0	0	0	0	0	0	0
502	3	8	11	11	11	3	8	11	5	5	2	8	10	0	0	0	1	0	1	1	0	0	0	0	0	0
TOTAL	344			332	162	152		315						0				17							0	0
MEAN	13.8			13.3	6.5	6.1		12.6						0.0				0.7							0.0	0.0
S.D.	1.8			1.5	2.1	1.9		1.5						0.0				0.9							0.0	0.0
N	25			25	25	25		25						25				25							25	25

NOTE: THE SEX OF FETUS 7 FROM DAM 435 WAS NOT RECORDED. THE TOTAL NUMBER OF VIABLE FETUSES INCLUDES THIS FETUS.

## APPENDIX B

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL CESAREAN SECTION DATA

GROUP 4: 30 MG BASE/KG/DAY

DAM#	CORPORA LUTEA		IMPLANTATIONS		SEX		VIABLE FETUSES		NONVIABLE FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS		
	LEFT	RIGHT	TOTAL	LEFT	RIGHT	TOTAL	LEFT	RIGHT	TOTAL	LEFT	RIGHT	TOTAL	LEFT	RIGHT	TOTAL
354	12	6	18	11	3	14	9	5	11	3	14	0	0	0	0
356	9	4	13	7	4	11	6	5	7	4	11	0	0	0	0
370	5	7	12	5	7	12	4	8	5	7	12	0	0	0	0
374	7	7	14	7	7	14	6	6	6	6	12	0	1	2	0
379	2	4	6	0	2	2	0	2	0	2	2	0	0	0	0
382	7	5	12	7	5	12	4	8	7	5	12	0	0	0	0
385	5	6	11	5	6	11	4	7	5	6	11	0	0	0	0
392	5	9	14	4	9	13	5	7	3	9	12	0	1	0	0
399	3	10	13	3	10	13	10	3	3	10	13	0	0	0	0
404	5	8	13	4	8	12	4	7	3	8	11	0	1	0	0
410	7	10	17	7	10	17	8	9	7	10	17	0	0	0	0
417	8	5	13	8	4	12	5	5	8	2	10	0	0	1	1
440	4	9	13	4	9	13	6	5	3	8	11	0	1	2	0
441	7	7	14	7	7	14	7	7	7	7	14	0	0	0	0
444	4	8	12	4	8	12	7	2	4	5	9	0	0	3	3
448	a	a	a	10	4	14	6	8	10	4	14	0	0	0	0
450	9	9	18	9	6	15	6	9	9	6	15	0	0	0	0
455	2	9	11	1	3	4	2	1	1	2	3	0	0	1	1
460	5	7	12	5	7	12	7	4	4	7	11	0	0	1	0
475	5	10	15	5	10	15	9	6	5	10	15	0	0	0	0
483	8	7	15	8	7	15	8	7	8	7	15	0	0	0	0
490	6	6	12	6	6	12	7	3	5	5	10	0	1	2	0
491	6	6	12	6	6	12	4	8	6	6	12	0	0	0	0
492	8	5	13	8	5	13	6	4	8	2	10	0	0	3	3
503	9	3	12	9	3	12	4	8	9	3	12	0	0	0	0
TOTAL	315		306	144	144	288									
MEAN	13.1		12.2	5.8	5.8	11.5				0			17		1
SD	2.5		3.1	2.3	2.3	3.3				0.0			0.7		0.0
N	24		25	25	25	25				25			25		25
--CORPORA LUTEA NOT RECORDED, NOT INCLUDED IN CALCULATIONS															

a=CORPORA LUTEA NOT RECORDED, NOT INCLUDED IN CALCULATIONS



## APPENDIX B

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL CESAREAN SECTION DATA

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

DAM#	CORPORA LUTEA		IMPLANTATIONS		SEX		VIABLE FETUSES		NONVIABLE FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS				
	LEFT	RIGHT	LEFT	RIGHT	M	F	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT			
353	8	5	13	8	5	13	8	3	7	4	11	0	0	1	0	1	0
362	12	7	19	9	6	15	6	5	6	5	11	0	0	3	1	4	0
364	6	8	14	5	4	13	4	5	4	5	9	0	0	1	3	4	0
366	12	5	17	12	5	14	5	5	9	1	10	0	0	3	1	4	0
368	8	6	14	8	4	14	4	10	8	6	14	0	0	0	0	0	0
372	7	12	19	4	9	13	6	6	4	8	12	0	0	0	1	1	0
389	7	6	13	2	4	6	4	2	2	4	6	0	0	0	0	0	0
391	3	10	13	3	10	13	3	10	3	10	13	0	0	0	0	0	0
401	6	6	12	6	3	12	3	5	3	5	8	0	0	3	1	4	0
407	5	8	13	5	8	13	5	6	5	6	11	0	0	0	2	2	0
422	11	4	15	10	4	14	8	4	8	4	12	0	0	2	0	2	0
423	8	5	13	7	5	12	5	6	6	5	11	0	0	1	0	1	0
426	4	9	13	4	9	13	7	5	4	8	12	0	0	0	1	1	0
430	7	6	13	7	6	13	5	7	7	5	12	0	0	0	1	1	0
432	10	9	19	6	7	13	6	7	6	7	13	0	0	0	1	1	0
442	7	8	15	7	8	15	3	10	6	7	13	0	0	0	0	0	0
445	5	10	15	5	10	15	6	7	3	10	13	0	0	1	1	2	0
465	5	7	12	5	6	11	6	3	4	5	9	0	0	1	0	1	1
468	3	9	12	3	9	12	2	7	2	7	9	0	0	1	1	2	0
476	5	7	12	4	7	11	5	5	4	6	10	0	0	1	2	3	0
477	8	8	16	8	7	15	8	5	7	6	13	0	0	0	1	1	0
485	7	9	16	6	7	13	9	2	5	6	11	0	0	1	1	2	0
493	6	10	16	5	10	15	4	0	2	2	4	0	0	3	8	11	0
496	11	5	16	9	4	13	5	8	9	4	13	0	0	0	0	0	0
499	7	10	17	6	7	13	2	6	4	4	8	0	0	2	2	4	1
TOTAL	367		324	129	139						268	0		53		3	
MEAN	14.7		13.0	5.2	5.5						10.7	0.0		2.1		0.1	
S.D.	2.3		1.9	1.8	2.5						2.4	0.0		2.3		0.3	
N	25		25	25	25						25	25		25		25	

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS  
 APPENDIX C  
 INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 1: 0 MG/KG/DAY																	
DAM #	GRAVID UTERUS WEIGHT	FETAL WEIGHT	INDIVIDUAL FETAL WEIGHT														
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
346	64.65	3.57	3.60M	E	3.75M	3.79F	3.64F	3.62M	3.26F	3.17F	3.61M	3.58M	3.72M	3.58F	3.54M	.	.
349	56.91	3.91	3.37M	4.06M	4.04F	3.56F	3.91F	4.05F	4.08M	4.07F	4.19M	3.74F	3.65F	3.79M	4.18M	.	.
352	72.12	3.81	3.60F	3.49F	4.05M	3.79F	3.64M	4.05M	3.60M	3.92M	3.79M	3.98F	3.65F	3.79M	4.18M	.	.
357	81.51	3.73	3.51F	3.67F	3.62M	3.91F	3.81F	3.84M	3.64F	3.96M	3.69F	3.93F	E	4.06M	3.80M	3.41F	3.45M
367	46.58	4.10	4.11M	3.98M	4.27M	4.00F	4.12M	4.28M	3.91M	.	.	.	.	.	.	.	.
369	68.25	3.70	3.75F	3.70F	4.04M	L	3.70F	3.39M	3.74F	3.70F	3.96F	3.64F	3.46F	3.58F	.	.	.
381	67.52	3.14	1.90M	2.16F	2.22F	2.06M	2.31F	3.21F	3.46F	4.06F	4.31M	3.71F	3.86F	3.81F	3.76F	.	.
386	64.76	3.82	3.81M	3.85M	3.80F	4.13M	3.56F	3.72F	3.84M	3.81M	3.68F	3.80M	4.05M	.	.	.	.
388	66.39	3.22	3.14F	3.22M	3.19F	3.24F	3.08F	3.62M	E	2.18F	3.50F	3.04M	3.10F	3.22F	3.48F	3.89M	.
396	73.03	3.68	3.72M	3.82F	3.95M	3.87M	3.87M	3.55M	3.19F	3.70M	3.79M	3.65F	3.59F	3.42M	3.68F	.	.
412	73.33	4.02	3.05F	4.00F	4.42F	3.66M	3.93F	4.35F	3.76F	4.25F	4.08F	4.27F	4.28M	4.14M	.	.	.
419	58.15	3.31	E	3.18F	3.25F	3.51M	3.46M	3.25F	3.21F	3.33F	E	3.22F	3.51F	3.40M	3.14M	E	.
421	72.83	3.67	3.63F	3.61F	3.76F	3.61M	3.73F	3.68F	3.30F	3.74M	3.97M	3.67F	3.72F	3.89M	3.39M	.	.
428	65.56	3.49	3.39F	3.22F	3.23F	3.30F	3.54F	3.67M	2.59F	3.13F	3.38F	3.72M	3.63M	3.56M	.	.	.
437	73.29	3.49	3.50F	3.65M	3.64F	3.81F	3.62M	3.64F	2.59F	3.13F	3.38F	3.72M	3.63M	3.56M	.	.	.
438	73.85	4.37	4.65M	4.16F	4.02M	4.12F	4.33F	3.97F	4.57M	4.56F	4.34M	4.70M	4.47M	4.60M	.	.	.
451	72.12	3.75	3.63F	3.81F	4.10M	3.73F	3.33F	3.51F	3.56M	3.87M	3.75M	4.19M	3.82F	3.71F	3.74F	.	.
452	84.67	3.96	4.18F	3.88M	3.82M	3.25M	3.90M	4.03M	3.95F	3.99M	3.86F	4.18M	4.05M	4.30M	3.86M	4.05M	4.07M
456	71.21	4.10	E	4.34M	4.17F	4.18F	3.59F	4.13M	3.88F	4.45M	4.06F	4.24M	4.25M	4.08M	3.80F	.	.
467	73.43	3.54	3.53M	3.42M	E	3.36F	3.60F	3.72M	3.48F	3.31M	3.12M	3.27F	L	3.97M	E	3.75M	3.60M
471	61.10	3.67	3.70M	3.63F	3.76M	3.62M	3.46M	3.40F	3.60F	3.98M	3.67F	3.89M	3.61F	.	.	.	.
474	70.22	3.46	3.25F	E	3.72F	3.28F	3.12M	3.74F	3.78F	3.43F	3.34F	3.13F	3.61M	E	3.72M	3.55M	3.30M
497	63.18	3.60	3.19F	3.55M	3.84M	3.48F	3.73M	3.76M	3.36M	3.72M	3.59F	3.45F	3.90F	.	.	.	.
500	78.43	3.70	3.41M	3.60M	3.78F	4.03M	3.30F	3.96M	3.94M	3.46M	3.70M	3.74M	E	3.81M	3.84M	3.53M	.
501	63.37	3.75	3.66M	3.67F	3.95M	3.75F	3.56F	3.72M	3.85M	4.10M	3.62F	3.74F	3.61F	.	.	.	.
MEAN	68.66	3.70															
S.D.	8.11	0.28															
N	25	25															

E= EARLY RESORPTION L= LATE RESORPTION  
 M=MALE F=FEMALE

# APPENDIX C

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 2: 3 MG BASE/KG/DAY

DAM #	GRAVID MEAN		INDIVIDUAL FETAL WEIGHT																
	UTERUS WEIGHT	FETAL WEIGHT	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
350	66.99	4.09	4.04M	4.15F	4.08M	4.04F	3.79M	4.03F	4.13F	4.21M	4.03F	4.26F	4.23M						
355	81.10	4.34	4.34F	4.13F	4.06F	4.11F	4.35F	4.28M	E	4.40M	4.36M	4.17M	4.51F	4.83M	4.53M	4.37M			
358	73.88	3.60	3.44F	3.42F	3.44F	3.53M	3.57F	3.77F	3.71M	3.58M	3.80M	3.49F	3.36F	3.72F	3.82F	3.71F			
360	70.01	3.89	3.67M	3.75F	3.78M	4.06M	3.94M	3.85M	3.85M	3.70F	4.06M	4.08F	3.80F	4.19M					
361	75.41	3.37	3.45M	3.28M	3.52M	3.36F	3.45M	3.36M	3.50M	3.37M	3.31F	3.43M	3.32F	3.14F	3.41M	3.23F			
376	73.58	4.13	4.20M	4.04M	4.22M	4.35M	3.94F	3.86F	4.45M	4.31M	3.79M	4.24M	4.02F	4.17F					
393	76.88	3.64	3.79M	3.59F	3.70M	3.77F	3.48F	3.78M	3.14F	3.40F	3.73F	3.89M	3.52F	3.87M	3.68F	3.61F			
398	67.20	3.68	4.01M	4.17F	3.28M	3.76M	3.89M	3.07F	3.47F	3.76M	3.64M	3.80F	3.59M	3.72M					
402	77.68	3.53	3.26M	3.85M	3.46F	3.56F	3.63M	3.33M	3.51F	3.31M	3.81M	3.76M	3.60M	3.60M	3.59M	3.41F	3.21F		
403	64.56	3.91	3.82F	4.03M	E	E	4.20M	3.64M	3.98M	4.05M	3.74F	3.93M	3.71F	3.89M	3.97M	3.74F			
405	80.00	3.67	3.87M	3.39F	3.65F	3.60F	3.95M	3.77M	3.54M	3.46F	3.55F	3.80F	3.58F	3.62F	3.82M	3.74F			
413	77.34	3.71	2.91F	3.68M	3.61M	3.41F	3.78M	3.93M	3.89M	4.01M	3.74M	3.67F	3.72M	3.78F	3.75F	4.01M			
415	67.05	3.68	3.52M	3.63F	3.74M	3.78F	E	3.58F	3.66F	3.39F	3.92M	3.72M	3.71F	3.60M	3.92F				
431	75.77	3.57	3.50F	3.70M	3.53F	3.78M	3.77F	3.39M	3.91M	3.36M	3.40F	3.50F	3.40F	3.50F	3.36F	3.88M			
436	69.20	3.57	3.19F	3.32F	3.71F	3.67M	3.74F	3.61F	L	3.62M	3.46F	3.62F	3.92M	3.44F					
439	87.37	4.04	3.92F	3.58M	3.83M	3.98F	4.09M	4.52M	4.00F	4.16M	3.97M	3.75F	4.29M	3.87F	4.26M	4.27M	4.16F		
449	83.15	3.90	3.85F	3.64F	3.60F	4.06M	3.93M	3.71F	3.80M	3.82M	3.81M	3.85F	4.16M	4.07M	4.28M	4.08M			
454	77.83	3.86	3.57M	3.91M	4.12M	4.02F	3.76M	3.61F	3.71F	3.82M	3.92M	3.90M	4.00M	4.08F	3.80F	3.96F			
462	70.77	3.64	3.58F	3.72M	3.72F	3.64M	3.85M	3.58F	E	E	3.74F	3.84F	3.69M	3.39F	3.50F	3.39F	3.65M		
473	68.40	3.75	3.66F	3.54F	E	4.13F	3.82F	3.64M	3.87M	3.54F	E	3.93M	3.77M	3.77M	3.52F	3.81M			
480	88.35	3.91	3.72F	4.04F	4.09M	4.02F	3.64F	3.91M	3.84M	3.59M	3.89F	4.03M	3.99M	3.97F	3.87F	4.33M	3.77F		
481	79.85	3.36	3.19F	3.16M	3.21F	3.46M	3.63F	3.43F	3.52F	2.68M	3.19F	3.43F	3.31F	3.64M	3.49M	3.57F	3.42F		
484	58.13	3.70	3.41F	3.45M	3.74M	3.75F	3.92M	E	4.02M	3.63F	3.65F	3.64F	3.75F	E					
489	79.97	4.00	3.94M	4.34M	4.30M	3.95F	4.50M	3.87M	3.67F	4.12M	3.89F	3.86F	4.09M	4.07M	3.37F				
495	59.41	3.44	2.71M	3.45M	3.40F	E	3.75M	3.21F	E	3.78M	3.33F	3.72M	3.46F	3.28F	3.73M				
MEAN	74.00	3.76																	
S.D.	7.79	0.25																	
N	25	25																	

E= EARLY RESORPTION L= LATE RESORPTION  
M=MALE F=FEMALE



## APPENDIX C

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 3: 10 MG BASE/KG/DAY

DAM #	GRAVID MEAN		INDIVIDUAL FETAL WEIGHT																
	UTERUS WEIGHT	FETAL WEIGHT	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
351	70.18	4.08	4.00F	4.57M	4.36M	4.43M	3.90F	4.15M	4.10F	3.86F	4.14M	3.72F	3.66F	3.73M	4.04F	3.85M	.	.	.
371	80.72	3.82	3.65F	3.80F	3.76F	3.65M	3.72F	3.72F	4.02M	3.81M	3.97M	3.73F	3.55F	3.73F	3.41M	.	.	.	.
378	69.58	3.60	3.60M	3.44F	3.69M	3.58F	3.77M	3.87M	3.27F	3.64F	3.25M	3.60F	3.94M	3.73F	3.41M	.	.	.	.
380	76.35	3.92	3.69F	4.18M	3.88F	4.13M	4.05M	3.95F	4.24M	3.48F	3.52M	4.08M	E	4.19M	3.72F	3.85M	.	.	.
383	59.71	4.01	4.09F	4.01M	3.73F	4.20F	3.93F	4.14F	4.03F	E	3.88F	4.12F	4.01F	.	.	.	.	.	.
384	86.06	4.16	3.72F	4.16M	4.37F	4.31M	4.22F	4.29M	4.01M	3.77M	4.37M	4.20M	4.29M	4.24F	4.10M	4.23M	.	.	.
390	70.94	3.51	3.25F	3.36F	3.72F	3.44F	3.51M	3.59M	3.70M	3.36M	3.45M	3.43F	3.55M	3.49F	3.81M	.	.	.	.
395	70.10	3.94	3.66F	3.69F	4.31M	3.79M	3.33M	3.72M	E	3.66F	4.26M	4.07M	4.30M	4.45M	4.06F	.	.	.	.
400	73.92	3.75	3.82F	3.68F	3.89M	3.75F	3.81F	3.65F	3.70F	3.70F	3.46F	3.88F	3.61M	3.92M	3.85F	.	.	.	.
420	79.48	3.33	3.00F	3.13F	3.41M	3.34F	3.26F	3.51M	3.35F	3.30M	3.27M	3.37F	3.19M	3.48F	3.48M	3.43M	3.46M	.	.
424	73.56	3.49	3.46F	3.25F	3.44M	3.45F	3.39F	3.36M	3.30F	3.55F	3.55M	3.44F	3.80M	3.49F	3.57F	3.83F	.	.	.
425	65.40	3.61	3.31F	3.80F	2.95M	3.57F	3.61F	3.75M	3.87M	3.79M	3.28F	3.82M	E	3.56F	3.97M	.	.	.	.
427	80.08	4.18	E	3.94F	4.16M	4.24M	4.42M	4.22F	4.23M	4.28F	3.81F	4.17M	4.14F	4.22F	4.31M	4.19M	.	.	.
434	79.28	3.77	3.62F	3.90F	3.96F	4.02M	3.83F	3.97M	3.63M	3.64F	3.59M	3.11F	3.75F	4.05M	3.78F	3.97F	E	.	.
435	56.63	3.63	3.43F	E	3.41F	3.80M	3.50F	E	3.65U	3.52M	3.60M	3.77M	3.78M	3.83M	E	.	.	.	.
447	80.63	4.21	3.79F	4.28F	4.48M	4.30F	4.43M	4.33F	3.69M	4.07M	4.21F	4.26M	4.41M	4.35M	4.15F	.	.	.	.
453	79.52	3.79	3.78M	E	4.00F	4.00F	3.74F	3.56F	4.06M	3.15F	3.70M	3.81M	3.93M	3.80F	3.91M	3.69F	3.85F	4.03M	.
457	71.84	4.05	4.24M	4.32M	4.14M	4.20M	3.44F	4.24M	3.97M	3.57F	3.87F	4.32M	E	3.95F	4.29M	.	.	.	.
459	83.81	3.73	3.55F	3.77M	E	3.73F	3.84M	3.66M	3.37M	3.75M	4.09M	3.67F	3.60F	3.81M	3.75F	3.74F	3.91M	3.73F	.
469	60.41	3.55	3.67M	3.59M	3.65M	3.63M	2.99F	3.42M	3.55F	3.72M	3.62F	3.67F	3.53F	3.57M	3.79M	3.74M	.	.	.
472	80.75	3.78	3.79M	3.80M	3.52F	4.02M	4.14M	3.83F	3.84F	3.79M	3.86M	3.67F	3.71M	3.57M	3.79M	3.74M	.	.	.
482	70.74	3.85	3.82M	3.60F	3.99F	3.76M	3.87M	3.59F	3.78F	3.91M	3.82F	4.08M	3.86F	4.13M	.	.	.	.	.
486	71.35	3.80	3.83M	3.89M	3.50F	3.69M	3.84F	3.91M	3.80M	4.13F	E	3.64F	3.14F	E	E	4.04M	4.15M	.	.
494	67.65	3.79	3.28F	3.98F	3.75F	3.68F	3.85F	3.75F	4.05M	3.58M	3.84M	3.67M	4.26M	.	.	.	.	.	.
502	56.50	3.53	3.65F	E	3.38F	3.29M	2.82F	3.34F	3.60M	3.83M	3.87M	3.65F	3.83M	.	.	.	.	.	.
MEAN	72.61	3.80																	
S.D.	8.29	0.23																	
N	25	25																	

E= EARLY RESORPTION L= LATE RESORPTION  
M=MALE F=FEMALE U=SEX NOT RECORDED



## APPENDIX C

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 4: 30 MG BASE/KG/DAY

DAM #	GRAVID MEAN		INDIVIDUAL FETAL WEIGHT																
	UTERUS WEIGHT	FETAL WEIGHT	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
354	76.71	3.46	3.45F	3.22M	3.61M	2.89M	3.59F	2.95M	3.60M	3.64M	3.68M	3.74F	3.62F	3.25F	3.50M	3.69M	.	.	.
356	66.77	3.94	3.83F	3.71M	3.85F	4.10M	4.21M	4.03M	3.86F	3.67F	4.07M	4.21M	3.76F	.	.	.	.	.	.
370	67.40	3.65	3.61M	3.41F	4.16M	3.90F	3.53M	3.62F	3.92F	3.70F	3.72F	2.31F	3.89F	4.01M	.	.	.	.	.
374	65.75	3.58	3.53M	3.74M	3.50M	3.46F	E	3.62F	3.71F	3.64F	3.69F	3.76F	E	3.61M	3.44M	3.29M	.	.	.
379	10.81	3.00	3.31F	2.68F	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
382	70.92	3.89	3.82F	3.93F	4.16M	3.28F	3.98F	3.80M	3.82F	4.19F	4.06M	4.18F	3.58F	3.89M	.	.	.	.	.
385	57.89	3.42	3.54M	3.37F	3.28F	3.62F	3.63M	3.13F	3.56M	3.20F	3.39F	3.59M	3.35F	.	.	.	.	.	.
392	66.91	3.63	3.50F	3.78F	E	3.96M	3.69M	3.68F	3.37F	3.92M	3.83M	3.84M	3.83F	3.25F	2.96F	.	.	.	.
399	74.58	3.88	3.79F	3.81F	3.77M	3.88M	3.91M	3.57F	3.95M	4.06M	4.03M	4.07M	3.89M	3.91M	3.84M	.	.	.	.
404	62.01	3.80	3.61F	3.99F	E	3.66F	3.76M	3.90M	4.09F	3.42M	4.26F	3.78F	3.82F	3.52M	.	.	.	.	.
410	94.02	3.58	3.79M	3.61F	3.42M	3.71M	3.58M	3.41M	3.87M	3.52M	3.74F	3.46F	3.49F	3.80F	3.67F	3.82F	3.00F	3.57M	3.37F
417	55.17	3.50	3.42F	3.37F	3.48F	3.36M	3.67M	3.42F	3.42M	3.61M	3.63M	3.57F	E	L	.	.	.	.	.
440	60.32	3.53	3.41F	3.66M	3.47F	E	3.31M	3.66M	E	3.60M	3.32F	3.59F	3.35F	3.58M	3.86M	.	.	.	.
441	75.13	3.56	3.87M	3.27F	3.34M	3.68F	3.78F	3.25F	3.67F	3.17F	3.67M	3.81M	3.80M	3.60M	3.50M	3.36F	.	.	.
444	51.77	3.71	3.30M	3.87M	3.58M	3.91M	3.73M	E	4.09M	3.57F	3.72M	3.61F	E	E	.	.	.	.	.
448	70.94	3.28	3.50M	3.69M	3.58F	3.60F	2.06F	3.16F	3.55M	3.32M	3.25M	3.16F	2.81F	3.38M	3.50F	3.32F	.	.	.
450	66.55	2.86	2.47M	2.87M	2.66F	2.66F	2.52F	2.49F	2.98M	3.07F	2.81F	3.06M	3.09M	3.09F	2.90F	3.22M	3.01F	.	.
455	20.75	4.00	3.81F	4.09M	E	4.10M	.	.	.	.	.	.	.	.	.	.	.	.	.
460	66.46	3.66	3.43F	3.55M	E	3.62F	3.78M	3.40M	3.71M	3.90M	3.68F	3.59M	3.92M	3.65F	.	.	.	.	.
475	72.46	3.31	3.55M	3.26M	3.51M	3.50F	3.43M	3.09F	3.23M	3.19M	3.25F	3.20F	3.48M	3.04F	3.05M	3.45M	3.35F	.	.
483	83.13	3.60	3.67M	3.44F	3.73F	3.90M	3.95M	3.51M	3.63M	3.38F	3.43F	3.76F	3.85M	3.84M	3.78F	3.45M	2.74F	.	.
490	54.40	3.47	3.30F	E	3.70M	3.42M	3.42M	3.34F	3.27F	3.58M	3.65M	3.57M	E	WM	.	.	.	.	.
491	78.17	4.11	3.57F	4.24M	4.29F	4.51M	4.03M	4.32F	3.75F	3.84F	3.95F	4.24F	4.28M	4.28F	.	.	.	.	.
492	50.71	3.18	3.10F	3.39M	3.14M	3.31M	3.25M	3.13F	3.17M	3.06F	E	2.85F	3.44M	E	E	.	.	.	.
503	67.01	3.71	3.36F	3.75M	3.44F	3.43F	3.74M	3.89F	3.83F	4.12M	3.67F	3.71F	3.35F	4.25M	.	.	.	.	.
MEAN	63.47	3.57																	
S.D.	17.48	0.30																	
N	25	25																	

E= EARLY RESORPTION L= LATE RESORPTION

M=MALE F=FEMALE

W=FETAL WEIGHT NOT RECORDED

## APPENDIX C

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RATS

INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

DAM #	GRAVID MEAN		INDIVIDUAL FETAL WEIGHT																
	UTERUS WEIGHT	FETAL WEIGHT	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
353	65.52	3.49	L	3.26M	3.52F	3.66M	3.42M	3.49M	3.29F	3.77M	E	3.64M	3.25F	3.55M	3.55M				
362	56.96	2.80	E	3.29M	3.29M	2.84F	3.23M	2.59M	3.05M	2.73F	E	3.48F	2.39F	E	3.01M	2.22F	1.94M		
364	55.63	3.02	3.13M	3.34F	E	2.97M	2.99F	E	3.25M	2.85F	E	2.73F	3.22M	E	2.71F				
366	51.85	3.09	2.63M	2.89F	3.77M	3.50M	2.94F	3.22M	2.35F	2.92F	E	E	E	3.59M	E	3.04F			
368	75.48	3.29	3.10F	2.37F	3.02F	3.76F	3.39F	3.09M	3.71M	3.14F	3.04F	3.28F	3.45M	3.34F	3.70M	3.66F			
372	54.84	2.65	2.34M	1.88F	2.61F	3.00M	2.94F	2.84M	E	2.66F	2.78F	2.52M	2.93M	2.93M	2.42F				
389	30.04	2.68	2.80M	2.56M	3.06M	2.21F	2.66M	2.79F											
391	72.98	3.75	3.81F	3.84F	3.96F	3.66F	3.53F	3.66M	3.78F	3.41F	3.92M	3.70F	3.99M	3.62F	3.84F				
401	46.87	3.27	E	3.24F	3.05M	E	3.96M	E	2.87F	E	3.07F	3.51F	3.51F	2.97M					
407	57.87	3.27	2.96M	3.75M	3.58M	3.03F	3.60M	E	2.97M	3.20F	E	3.38F	3.13F	3.08F	3.31F				
422	62.05	3.24	2.81F	3.20M	2.99M	3.22M	E	3.44M	3.30M	E	2.58F	3.32M	3.58M	3.65M	3.17F	3.56F			
423	64.69	3.93	E	3.94M	3.32F	4.09M	4.01M	3.88F	4.11F	3.76F	4.05F	4.27M	3.87F	3.97M					
426	69.79	3.79	3.41F	2.95M	4.10M	4.15F	3.52M	E	3.69F	3.75M	3.82M	3.82M	4.17M	4.06F					
430	67.30	3.48	2.89F	3.93M	3.51F	3.54F	3.36F	3.69M	3.46M	3.31M	3.45F	3.54M	3.53F	E	3.98F				
432	74.11	3.44	3.24M	2.90M	3.39M	2.99M	3.52F	3.58F	3.51M	3.45F	3.75M	3.41F	3.15F	4.02F					
442	67.02	3.29	2.83F	3.50M	E	2.97F	3.88M	3.08F	3.60F	3.05F	3.13F	3.15F	3.35F	E	3.30F	3.73M	3.26F		
445	77.55	3.67	3.77M	3.81M	E	3.38F	L	3.22F	3.51F	3.26F	3.95M	3.68F	3.97M	3.76F	3.91M	3.78F	3.73M		
465	48.17	2.96	2.78M	3.28M	E	2.82F	E	2.59F	2.99M	3.22M	2.77M	2.63F	E						
468	41.27	2.66	2.58F	E	3.06	2.55M	1.79F	3.22F	2.91F	E	2.88F	2.50F	2.49F	E					
476	61.30	3.32	3.67M	3.39M	3.27M	3.45M	2.90F	2.96M	E	3.79M	3.24F	3.14F	3.35F						
477	66.33	3.24	E	3.35M	3.30M	2.70F	3.35F	3.17M	3.60M	3.13F	3.03M	3.48M	2.72F	3.41M	3.41M	3.53F	E		
485	54.63	3.01	2.58M	E	3.12M	2.51F	3.39M	3.28M	3.48M	E	2.53M	2.85M	3.46F	2.98M	2.90M				
493	24.94	3.06	E	3.30M	E	3.30M	E	E	E	E	2.43M	E	3.40M	E	E	E	E		
496	69.81	3.30	2.58F	3.32F	3.51M	3.75M	3.75F	3.47F	3.36F	3.80M	3.02F	2.52M	3.52M	2.84F	2.43F				
499	44.45	2.75	E	2.48M	2.93F	2.49F	E	2.89F	E	L	2.83F	E	2.83F	2.85M	2.72F				
MEAN	58.46	3.22																	
S.D.	13.59	0.36																	
N	25	25																	

E= EARLY RESORPTION L= LATE RESORPTION  
M=MALE F=FEMALE

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 346

Fetal Position: Left 03 Unique Fetal Id.: 3  
RIBS (Skeletal) RIB(S), BENT, SLIGHT TO MODERATE - VARIATION; RIGHT 12, SLIGHT

Fetal Position: Right 01 Unique Fetal Id.: 7  
STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Right 03 Unique Fetal Id.: 9  
STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT

Fetal Position: Right 07 Unique Fetal Id.: 13  
STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

Animal: 349

Fetal Position: Left 01 Unique Fetal Id.: 1  
STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Right 02 Unique Fetal Id.: 5  
STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT

Animal: 352

Fetal Position: Left 02 Unique Fetal Id.: 2  
STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 352 (CONT.)

Fetal Position: STERNUM (Skeletal)	Left 04	Unique Fetal Id.: 4
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, SLIGHT	
Fetal Position: STERNUM (Skeletal)	Left 06	Unique Fetal Id.: 6
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, SLIGHT	
Fetal Position: STERNUM (Skeletal)	Right 06	Unique Fetal Id.: 12
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT	

Animal: 357

Fetal Position: SKULL (Skeletal)	Left 03	Unique Fetal Id.: 3
	HYOID, UNOSSIFIED - VARIATION	
Fetal Position: STERNUM (Skeletal)	Right 01	Unique Fetal Id.: 7
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT	
Fetal Position: STERNUM (Skeletal)	Right 06	Unique Fetal Id.: 12
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT	
Fetal Position: STERNUM (Skeletal)	Right 08	Unique Fetal Id.: 14
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT	



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 367

Fetal Position:	Left 03	Unique Fetal Id.: 3
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT	

Animal: 369

Fetal Position:	Right 01	Unique Fetal Id.: 6
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT	
	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	

Fetal Position:	Right 03	Unique Fetal Id.: 8
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT	

Fetal Position:	Right 07	Unique Fetal Id.: 12
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	

Animal: 381

Fetal Position:	Left 01	Unique Fetal Id.: 1
PELVIS		
(Skeletal)	PUBIS, UNOSSIFIED - VARIATION; BILATERAL	

STERNUM (Skeletal)	STERNEBRA(E), 1-4, UNOSSIFIED - VARIATION STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION
--------------------	---

VERTEBRAL COLUMN (Skeletal)	CERVICAL ARCHES, REDUCED OSSIFICATION - VARIATION; RIGHT 4-7
-----------------------------	--

SKULL (Skeletal)	SUPRAOCCIPITAL, REDUCED OSSIFICATION - VARIATION; SLIGHT HYOID, UNOSSIFIED - VARIATION
------------------	--

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 381 (CONT.)

Fetal Position:	Left 03	Unique Fetal Id.: 3
STERNUM		
(Skeletal)		STERNEBRA(E), 1-4, UNOSSIFIED - VARIATION; 2 AND 3 ONLY STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

### HINDLIMBS

(Skeletal) TARSALS, UNOSSIFIED - VARIATION; BILATERAL, ONLY 3 OSSIFIED

Fetal Position:	Left 05	Unique Fetal Id.: 5
STERNUM		
(Skeletal)		STERNEBRA(E), 1-4, UNOSSIFIED - VARIATION; 4 ONLY STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

### HINDLIMBS

(Skeletal) TARSALS, UNOSSIFIED - VARIATION; BILATERAL, ONLY 3 OSSIFIED

Animal: 388

Fetal Position:	Left 08	Unique Fetal Id.: 8
HEAD		
(External)		HEAD, MICROCEPHALY - MALFORMATION
(Visceral)		HEAD, CONFIRMATION OF EXTERNAL FINDINGS - CONFIRMATION; FACIAL APLASIA AND SMALL
(External)		HEAD: AGLOSSIA, HEAD UNDERDEVELOPED, NO NASAL TURBINATES, ANOPHTHALMIA
		FACE, FACIAL APLASIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 396

Fetal Position: ABDOMEN (Visceral)	Left 01	Unique Fetal Id.: 1
		KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, MODERATE
Fetal Position: STERNUM (skeletal)	Left 02	Unique Fetal Id.: 2
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT
Fetal Position: SKULL (skeletal)	Left 04	Unique Fetal Id.: 4
		HYOID, UNOSSIFIED - VARIATION
Fetal Position: SKULL (Skeletal)	Right 01	Unique Fetal Id.: 6
		HYOID, UNOSSIFIED - VARIATION
Fetal Position: ABDOMEN (Visceral)	Right 06	Unique Fetal Id.: 11
		KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, SLIGHT
Fetal Position: ANUS (External)	Right 07	Unique Fetal Id.: 12
		ANAL OPENING, SMALL IN SIZE - MALFORMATION
TAIL (External) (Skeletal)		TAIL, SHAPE, SMALL FLESHY TAB - MALFORMATION CONFIRMATION OF TAIL ANOMALY - CONFIRMATION; SACRAL VERTEBRA 2, MALFORMED; SACRAL VERTEBRAE 3-4 AND ALL CAUDAL VERTEBRAE ABSENT
Fetal Position: ABDOMEN (Visceral)	Right 08	Unique Fetal Id.: 13
		KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, MODERATE

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 412

Fetal Position: Left 01 Unique Fetal Id.: 1  
HEAD

(External) BRAIN, EXENCEPHALY - MALFORMATION  
(Visceral) BRAIN, HEMORRHAGE - MALFORMATION; MODERATE

Fetal Position: Right 02 Unique Fetal Id.: 8  
STERNUM  
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT

Animal: 428

Fetal Position: Left 02 Unique Fetal Id.: 2  
STERNUM  
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT STERNEBRA(E),  
5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Left 04 Unique Fetal Id.: 4  
STERNUM  
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Left 06 Unique Fetal Id.: 6  
STERNUM  
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, SLIGHT

Fetal Position: Right 01 Unique Fetal Id.: 8  
STERNUM  
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT

Fetal Position: Right 05 Unique Fetal Id.: 12  
STERNUM  
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 437

Fetal Position: STERNUM (Skeletal)	Left 01	Unique Fetal Id.: 1
		STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 01	Unique Fetal Id.: 7
		STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: SKULL (Skeletal)	Right 07	Unique Fetal Id.: 13
		HYOID, UNOSSIFIED - VARIATION

Animal: 438

Fetal Position: STERNUM (Skeletal)	Left 02	Unique Fetal Id.: 2
		STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT
Fetal Position: STERNUM (Skeletal)	Left 04	Unique Fetal Id.: 4
		STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 03	Unique Fetal Id.: 8
		STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT
Fetal Position: RIBS (Skeletal)	Right 05	Unique Fetal Id.: 10
		RIB(S), BENT, SLIGHT TO MODERATE - VARIATION; RIGHT 4 AND 11, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 07	Unique Fetal Id.: 12
		STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 451

Fetal Position:	Right 09	Unique Fetal Id.: 13
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT	

Animal: 452

Fetal Position:	Left 04	Unique Fetal Id.: 4
SKULL		
(Skeletal)	SKULL, CONFIRMATION OF EXTERNAL FINDINGS - CONFIRMATION; MICROGNATHIA (MAXILLAE AND MANDIBULAR): MANDIBLE BILATERAL--FUSED AND SMALL IN SIZE, PREMAXILLAE BILATERAL--SMALL IN SIZE, NASAL BONES--FUSED AND SMALL IN SIZE; CLEFT PALATE	

### HEAD

(External) MOUTH, PALATE, CLEFT PALATE - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION JAW, MANDIBLE, MICROGNATHIA - MALFORMATION

Unique Fetal Id.: 8

Fetal Position: Left 08

SKULL

(Skeletal) SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; RIGHT, SLIGHT

Unique Fetal Id.: 9

Fetal Position: Right 01

ABDOMEN

(Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT URETER(S), HYDROURETER - VARIATION; BILATERAL, SLIGHT

Animal: 456

Fetal Position:	Right 03	Unique Fetal Id.: 7
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT	

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 467

Fetal Position: Left 06 Unique Fetal Id.: 6  
 RIBS (skeletal) RIB(S), BENT, SLIGHT TO MODERATE - VARIATION; RIGHT 5 AND 11  
 STERNUM (skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT

Fetal Position: Right 01 Unique Fetal Id.: 8  
 STERNUM (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

Fetal Position: Right 03 Unique Fetal Id.: 10  
 RIBS (skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT

STERNUM (skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

Fetal Position: Right 09 Unique Fetal Id.: 16  
 RIBS (skeletal) RIB(S), BENT, SLIGHT TO MODERATE - VARIATION; LEFT 6-11; RIGHT 3-12

Animal: 471

Fetal Position: Left 03 Unique Fetal Id.: 3  
 STERNUM (skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Right 01 Unique Fetal Id.: 5  
 STERNUM (skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 AND 6

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 474

Fetal Position: Left 03 Unique Fetal Id.: 3  
 STERNUM (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Left 07 Unique Fetal Id.: 7  
 STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT

Animal: 497

Fetal Position: Left 01 Unique Fetal Id.: 1  
 SKULL (Skeletal) SUPRAOCCIPITAL, REDUCED OSSIFICATION - VARIATION; SLIGHT INTERPARIETAL, REDUCED OSSIFICATION - VARIATION; SLIGHT HYOID, UNOSSIFIED - VARIATION

Fetal Position: Left 03 Unique Fetal Id.: 3  
 RIBS (Skeletal) RIB(S), BENT, SLIGHT TO MODERATE - VARIATION; LEFT 5-9 AND 11; RIGHT 5-11

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT

SKULL (Skeletal) HYOID, UNOSSIFIED - VARIATION PARIETAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SLIGHT SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; RIGHT, SLIGHT

Fetal Position: Left 05 Unique Fetal Id.: 5  
 STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 497 (CONT.)  
 Fetal Position: Right 01 Unique Fetal Id.: 7  
 STERNUM (Skeletal)  
 STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT  
 STERNEBRA(E), 1-4, UNOSSIFIED - VARIATION; 2 ONLY

SKULL (Skeletal)  
 INTERPARIETAL, REDUCED OSSIFICATION - VARIATION; SLIGHT HYOID, UNOSSIFIED -  
 VARIATION PARIETAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SLIGHT  
 SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SLIGHT

Animal: 500  
 Fetal Position: Left 04 Unique Fetal Id.: 4  
 STERNUM (Skeletal)  
 STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT

Fetal Position: Left 06 Unique Fetal Id.: 6  
 STERNUM (Skeletal)  
 STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT  
 Fetal Position: Right 01 Unique Fetal Id.: 8  
 SKULL (Skeletal)  
 PARIETAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SLIGHT

Animal: 501  
 Fetal Position: Left 01 Unique Fetal Id.: 1  
 STERNUM (Skeletal)  
 STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT  
 SKULL (Skeletal)  
 HYOID, UNOSSIFIED - VARIATION

APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 501 (CONT.)		
Fetal Position: STERNUM (Skeletal)	Right 01	Unique Fetal Id.: 5
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM (Skeletal)	Right 07	Unique Fetal Id.: 11
		STERNEBRA(E), 1-4, UNOSSIFIED - VARIATION; 2,3, AND 4 ONLY STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 AND 6

NOTE: THE FETUSES FROM LITTERS 388, 419, AND 421 SCHEDULED FOR SKELETAL EXAMINATION DISARTICULATED DURING PROCESSING. INDIVIDUAL FETAL SKELETAL EXAMINATIONS WERE NOT POSSIBLE.

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 350

Fetal Position:	Left 04	Unique Fetal Id.: 4
STERNUM		
(Skeletal)		
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT	
Fetal Position:	Right 06	Unique Fetal Id.: 10
RIBS		
(Skeletal)		
	RIB 14, RUDIMENTARY - VARIATION; BILATERAL	
STERNUM		
(Skeletal)		
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT	

Animal: 355

Fetal Position:	Right 02	Unique Fetal Id.: 10
STERNUM		
(Skeletal)		
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT	

Animal: 358

Fetal Position:	Left 02	Unique Fetal Id.: 2
STERNUM		
(Skeletal)		
	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position:	Left 04	Unique Fetal Id.: 4
STERNUM		
(Skeletal)		
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT	
Fetal Position:	Left 06	Unique Fetal Id.: 6
STERNUM		
(Skeletal)		
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT	

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 358 (CONT.)

Fetal Position: STERNUM (Skeletal)	Left 08	Unique Fetal Id.: 8
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT
Fetal Position: STERNUM (Skeletal)	Left 10	Unique Fetal Id.: 10
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT
		STERNEBRA(E), 5-6, UNOSSFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM (Skeletal)	Right 02	Unique Fetal Id.: 12
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT STERNEBRA(E),
		5-6, UNOSSFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM (Skeletal)	Right 04	Unique Fetal Id.: 14
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT
		STERNEBRA(E), 5-6, UNOSSFIED - VARIATION; 5 ONLY

Animal: 360

Fetal Position: STERNUM (Skeletal)	Right 01	Unique Fetal Id.: 6
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 05	Unique Fetal Id.: 10
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 361

Fetal Position: Left 03 Unique Fetal Id.: 3  
STERNUM  
(skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY

Fetal Position: Left 05 Unique Fetal Id.: 5  
STERNUM  
(skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT  
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Left 07 \* Unique Fetal Id.: 7

Comments: FETUSES 7 AND 13 WERE INADVERTENTLY SEPARATED FROM THEIR TAGS FOLLOWING THE EXTERNAL EXAMS BUT PRECEDING THE SKELETAL EXAMS; THEREFORE, SKELETAL FINDINGS FOR THESE TWO FETUSES MAY BE ASSIGNED INCORRECTLY.

Fetal Position: Right 06 \* Unique Fetal Id.: 13

Comments: SEE COMMENT ON FETUS 7.

STERNUM  
(skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT

Animal: 376

Fetal Position: Right 01 Unique Fetal Id.: 8  
STERNUM  
(skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3,4 AND 5, SLIGHT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 376 (CONT.)

Fetal Position: Right 02 \* Unique Fetal Id.: 9

Comments: PALE SKIN COLORATION NOT EVIDENT AT BOVINS (Visceral) EXAM

WHOLE BODY  
(External)

WHOLE BODY, PALLID FETUS - VARIATION

Fetal Position: Right 05

Unique Fetal Id.: 12

STERNUM  
(Skeletal)

STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

Animal: 398

Fetal Position: Left 01

Unique Fetal Id.: 1

ABDOMEN  
(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, MODERATE

Fetal Position: Left 05

Unique Fetal Id.: 5

ABDOMEN  
(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; LEFT, MODERATE

Fetal Position: Left 06

Unique Fetal Id.: 6

RIBS  
(Skeletal)

RIB(S), BENT, SLIGHT TO MODERATE - VARIATION; LEFT 11, RIGHT 6, 7 AND 11, SLIGHT

STERNUM  
(Skeletal)

STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

Fetal Position: Right 01

Unique Fetal Id.: 7

ABDOMEN  
(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, MODERATE

Fetal Position: Right 02

Unique Fetal Id.: 8

SKULL  
(Skeletal)

SUPRAOCCIPITAL, REDUCED OSSIFICATION - VARIATION; SLIGHT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 398 (CONT.)

Fetal Position: Right 04 Unique Fetal Id.: 10  
STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT

Fetal Position: Right 05 Unique Fetal Id.: 11  
ABDOMEN (Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SEVERE

Fetal Position: Right 06 Unique Fetal Id.: 12  
STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT

SKULL (Skeletal) HYOID, UNOSSIFIED - VARIATION

Animal: 403

Fetal Position: Left 01 Unique Fetal Id.: 1  
STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT

Fetal Position: Left 05 Unique Fetal Id.: 5  
STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

Fetal Position: Right 02 Unique Fetal Id.: 7  
STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

Animal: 413

Fetal Position: Left 01 Unique Fetal Id.: 1  
WHOLE BODY (External) WHOLE BODY, PALLID FETUS - VARIATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 415

Fetal Position: STERNUM (Skeletal)	Right 01	Unique Fetal Id.: 8
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT
Fetal Position: SKULL (Skeletal)	Right 03	Unique Fetal Id.: 10
		HYOID, UNOSSIFIED - VARIATION

Animal: 431

Fetal Position: STERNUM (Skeletal)	Left 01	Unique Fetal Id.: 1
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 02	Unique Fetal Id.: 9
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM (Skeletal)	Right 06	Unique Fetal Id.: 13
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE/RIBS, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; THORACIC ARCH 12, LEFT--SMALL; THORACIC ARCHES 11 AND 13, LEFT--LARGE; THORACIC CENTRUM 11--MALALIGNED; THORACIC CENTRUM 12--FORMED ON RIGHT SIDE ONLY; THORACIC CENTRUM 13--BIPARTITE AND MALALIGNED; RIB 12, LEFT, ARTICULATING HEAD--SMALL



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 436

Fetal Position: STERNUM	Left 06	Unique Fetal Id.: 6
(Skeletal)	STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT	
Fetal Position: STERNUM	Right 02	Unique Fetal Id.: 9
(Skeletal)	STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position: STERNUM	Right 04	Unique Fetal Id.: 11
(Skeletal)	STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT	

Animal: 439

Fetal Position: STERNUM	Right 03	Unique Fetal Id.: 11
(Skeletal)	STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT	
Fetal Position: STERNUM	Right 07	Unique Fetal Id.: 15
(Skeletal)	STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT	

Animal: 449

Fetal Position: STERNUM	Left 05	Unique Fetal Id.: 5
(Skeletal)	STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position: STERNUM	Left 07	Unique Fetal Id.: 7
(Skeletal)	STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	

SKULL (Skeletal) HYOID, UNOSSIFIED - VARIATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 449 (CONT.)

Fetal Position:	Left 09	Unique Fetal Id.: 9
RIBS	(Skeletal)	RIB(S), BENT, SLIGHT TO MODERATE - VARIATION; RIGHT 5, 6 AND 7, SLIGHT
STERNUM	(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT
Fetal Position:	Right 04	Unique Fetal Id.: 13
RIBS	(Skeletal)	RIB 14, RUDIMENTARY - VARIATION; BILATERAL
STERNUM	(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT

Animal: 454

Fetal Position:	Left 04	Unique Fetal Id.: 4
STERNUM	(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT
Fetal Position:	Right 04	Unique Fetal Id.: 8
STERNUM	(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

Animal: 462

Fetal Position:	Right 02	Unique Fetal Id.: 6
STERNUM	(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position:	Right 10	Unique Fetal Id.: 14
STERNUM	(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 480

Fetal Position: STERNUM (Skeletal)	Left 04	Unique Fetal Id.: 4
		STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 02	Unique Fetal Id.: 8
		STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM (Skeletal)	Right 06	Unique Fetal Id.: 12
		STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Animal: 481

Fetal Position: STERNUM (Skeletal)	Left 03	Unique Fetal Id.: 3
		STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM (Skeletal)	Left 05	Unique Fetal Id.: 5
		STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM (Skeletal)	Right 03	Unique Fetal Id.: 11
		STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY
Fetal Position: STERNUM (Skeletal)	Right 05	Unique Fetal Id.: 13
		STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4 STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 481

Fetal Position:	Right 07	Unique Fetal Id.: 15
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT	

Animal: 484

Fetal Position:	Left 04	Unique Fetal Id.: 4
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position:	Right 02	Unique Fetal Id.: 9
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3,4 AND 5, SLIGHT	
Fetal Position:	Right 04	Unique Fetal Id.: 11
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	

Animal: 489

Fetal Position:	Left 01	Unique Fetal Id.: 1
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT	
Fetal Position:	Right 08	Unique Fetal Id.: 13
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT	
	STERNEBRA(E), 1-4, UNOSSIFIED - VARIATION; 4 ONLY STERNEBRA(E), 5-6, UNOSSIFIED	
	- VARIATION; 5 ONLY	



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 3 MG BASE/KG/DAY

Animal: 495

Fetal Position: STERNUM	Left 01	Unique Fetal Id.: 1
(Skeletal)		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM	Left 06	Unique Fetal Id.: 6
(Skeletal)		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM	Left 09	Unique Fetal Id.: 9
(Skeletal)		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, SLIGHT
Fetal Position: RIBS	Right 04	Unique Fetal Id.: 13
(Skeletal)		RIB(S), BENT, SLIGHT TO MODERATE - VARIATION; LEFT 10, 11 AND 12; RIGHT 9-12; SLIGHT

NOTE: THE FETUSES FROM LITTERS 393, 402, 405 AND 413 SCHEDULED FOR SKELETAL EXAMINATION DISARTICULATED DURING PROCESSING. INDIVIDUAL FETAL SKELETAL EXAMINATIONS WERE NOT POSSIBLE.

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 10 MG BASE/KG/DAY

Animal: 351

Fetal Position: STERNUM (Skeletal)	Left 03	Unique Fetal Id.: 3
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT
Fetal Position: STERNUM (Skeletal)	Left 05	Unique Fetal Id.: 5
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 02	Unique Fetal Id.: 11
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Animal: 371

Fetal Position: STERNUM (Skeletal)	Left 01	Unique Fetal Id.: 1
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY
Fetal Position: STERNUM (Skeletal)	Right 02	Unique Fetal Id.: 7
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 08	Unique Fetal Id.: 13
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

Animal: 378

Fetal Position: STERNUM (Skeletal)	Left 02	Unique Fetal Id.: 2
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, SLIGHT
Fetal Position: STERNUM (Skeletal)	Left 06	Unique Fetal Id.: 6
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 10 MG BASE/KG/DAY

Animal: 378 (CONT.)

Fetal Position: Left 08 Unique Fetal Id.: 8  
 STERNUM  
 (Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

Animal: 380

Fetal Position: Left 02 Unique Fetal Id.: 2  
 STERNUM  
 (Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT  
 STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Left 04 Unique Fetal Id.: 4  
 STERNUM  
 (Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

Fetal Position: Right 01 Unique Fetal Id.: 8  
 STERNUM  
 (Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT

Fetal Position: Right 06 Unique Fetal Id.: 13  
 STERNUM  
 (Skeletal) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Animal: 383

Fetal Position: Left 01 Unique Fetal Id.: 1  
 STERNUM  
 (Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

Fetal Position: Left 03 Unique Fetal Id.: 3  
 STERNUM  
 (Skeletal) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Left 05 Unique Fetal Id.: 5  
 STERNUM (Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 10 MG BASE/KG/DAY

Animal: 383 (CONT.)

Fetal Position:	Right 01	Unique Fetal Id.: 7
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT	

Animal: 384

Fetal Position:	Left 02	Unique Fetal Id.: 2
SKULL		
(Skeletal)	HYOID, UNOSSIFIED - VARIATION	
Fetal Position:	Left 04	Unique Fetal Id.: 4
RIBS		
(Skeletal)	RIB 13, REDUCED OSSIFICATION - VARIATION; LEFT	
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT	
Fetal Position:	Right 02	Unique Fetal Id.: 8
RIBS		
(Skeletal)	RIB 13, REDUCED OSSIFICATION - VARIATION; RIGHT	
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
SKULL		
(Skeletal)	HYOID, UNOSSIFIED - VARIATION	
Fetal Position:	Right 04	Unique Fetal Id.: 10
RIBS		
(Skeletal)	RIB 13, REDUCED OSSIFICATION - VARIATION; BILATERAL	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 25 PRESACRAL VERTEBRAE - VARIATION	
SKULL		
(Skeletal)	HYOID, UNOSSIFIED - VARIATION	



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 10 MG BASE/KG/DAY

Animal: 384 (CONT.)

Fetal Position: STERNUM (Skeletal)	Right 06	Unique Fetal Id.: 12
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT
Fetal Position: RIBS (Skeletal)	Right 08	Unique Fetal Id.: 14
		RIB 13, REDUCED OSSIFICATION - VARIATION; BILATERAL
VERTEBRAL COLUMN (Skeletal)		VERTEBRAE, 25 PRESACRAL VERTEBRAE - VARIATION

Animal: 390

Fetal Position: STERNUM (Skeletal)	Left 04	Unique Fetal Id.: 4
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM (Skeletal)	Left 08	Unique Fetal Id.: 8
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM (Skeletal)	Right 02	Unique Fetal Id.: 10
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
SKULL (Skeletal)		HYOID, UNOSSIFIED - VARIATION

Animal: 395

Fetal Position: STERNUM (Skeletal)	Left 01	Unique Fetal Id.: 1
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 10 MG BASE/KG/DAY

Animal: 395 (CONT.)

Fetal Position: Right 02 Unique Fetal Id.: 5  
SKULL (Skeletal) HYOID, UNOSSIFIED - VARIATION

Fetal Position: Right 09 Unique Fetal Id.: 12  
STERNUM (Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT

Animal: 420

Fetal Position: Left 02 Unique Fetal Id.: 2  
STERNUM (Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

Fetal Position: Left 04 Unique Fetal Id.: 4  
STERNUM (Skeletal) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Right 01 Unique Fetal Id.: 8  
STERNUM (Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT STERNEBRA (E),  
5-6, UNOSSIFIED - VARIATION; 5 ONLY

SKULL (Skeletal) HYOID, UNOSSIFIED - VARIATION

Fetal Position: Right 07 Unique Fetal Id.: 14  
STERNUM (Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT STERNEBRA (E),  
5-6, UNOSSIFIED - VARIATION; 5 ONLY

Animal: 427

Fetal Position: Left 04 Unique Fetal Id.: 4

STERNUM (Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3,4 AND 5, SLIGHT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 10 MG BASE/KG/DAY

Animal: 427 (CONT.)

Fetal Position: STERNUM (Skeletal)	Left 06	Unique Fetal Id.: 6
		STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 06	Unique Fetal Id.: 12
		STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT

Animal: 434

Fetal Position: STERNUM (Skeletal)	Right 02	Unique Fetal Id.: 8
		STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2,3 AND 4, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 04	Unique Fetal Id.: 10
		STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2,3 AND 4, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 06	Unique Fetal Id.: 12
		STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT

Animal: 435

Fetal Position: STERNUM (Skeletal)	Left 04	Unique Fetal Id.: 4
		STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3,4 AND 5, SLIGHT
Fetal Position: RIBS (Skeletal)	Left 07	Unique Fetal Id.: 7
		RIB(S), BENT, SLIGHT TO MODERATE - VARIATION; BILATERAL 11 AND 12
SKULL (Skeletal)		SUPRAOCCIPITAL, REDUCED OSSIFICATION - VARIATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 10 MG BASE/KG/DAY

Animal: 447

Fetal Position: STERNUM (Skeletal)	Left 03	Unique Fetal Id.: 3
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3,4 AND 5, SLIGHT
Fetal Position: STERNUM (Skeletal)	Left 05	Unique Fetal Id.: 5
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT
Fetal Position: RIBS (Skeletal)	Right 01	Unique Fetal Id.: 7
		RIB 13, RUDIMENTARY - VARIATION; LEFT
VERTEBRAL COLUMN (Skeletal)		VERTEBRAE, 25 PRESACRAL VERTEBRAE - VARIATION

Animal: 453

Fetal Position: RIBS (Skeletal)	Left 01	Unique Fetal Id.: 1
		RIB 13, REDUCED OSSIFICATION - VARIATION; LEFT
STERNUM (Skeletal)		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM (Skeletal)	Left 05	Unique Fetal Id.: 5
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: RIBS (Skeletal)	Left 07	Unique Fetal Id.: 7
		RIB(S), BENT, SLIGHT TO MODERATE - VARIATION; RIGHT 6-9, SLIGHT
STERNUM (Skeletal)		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 10 MG BASE/KG/DAY

Animal: 453 (CONT.)

Fetal Position: Left 08 Unique Fetal Id.: 8  
ABDOMEN  
(Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, SLIGHT

Fetal Position: Right 01 Unique Fetal Id.: 9  
STERNUM  
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT

Fetal Position: Right 03 Unique Fetal Id.: 11  
STERNUM  
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT

Fetal Position: Right 04 Unique Fetal Id.: 12  
ABDOMEN  
(Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, SLIGHT

Fetal Position: Right 05 Unique Fetal Id.: 13  
RIBS  
(Skeletal) RIB(S), BENT, SLIGHT TO MODERATE - VARIATION; LEFT 5, 6 AND 7, 10-13; RIGHT, 4-13

STERNUM  
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Right 07 Unique Fetal Id.: 15  
STERNUM  
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT STERNEBRA(E),  
5-6, UNOSSIFIED - VARIATION; 5 ONLY

Animal: 457

Fetal Position: Left 02 Unique Fetal Id.: 2  
ABDOMEN  
(Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; LEFT, SLIGHT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 10 MG BASE/KG/DAY

Animal: 457 (CONT.)

Fetal Position: ABDOMEN (Visceral)	Left 04	Unique Fetal Id.: 4
		KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, MODERATE URETER(S), HYDROURETER - VARIATION; LEFT, MODERATE
Fetal Position: ABDOMEN (Visceral)	Right 02	Unique Fetal Id.: 6
		KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, SLIGHT
Fetal Position: RIBS (Skeletal)	Right 05	Unique Fetal Id.: 9
		RIB 13, RUDIMENTARY - VARIATION; RIGHT

VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, 25 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: RIBS (Skeletal)	Right 08	Unique Fetal Id.: 12
		RIB 13, RUDIMENTARY - VARIATION; BILATERAL
Fetal Position: ABDOMEN (Visceral)	Right 09	Unique Fetal Id.: 13
		KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT

Animal: 459

Fetal Position: STERNUM (Skeletal)	Left 01	Unique Fetal Id.: 1
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM (Skeletal)	Left 04	Unique Fetal Id.: 4
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 10 MG BASE/KG/DAY

Animal: 459 (CONT.)

Fetal Position: STERNUM (Skeletal)	Right 01	Unique Fetal Id.: 6
	STERNEBRA (E),	MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 05	Unique Fetal Id.: 10
	STERNEBRA (E),	MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT
	STERNEBRA (E),	5-6, UNOSSFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM	Right 07	Unique Fetal Id.: 12
	STERNEBRA (E),	MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 09	Unique Fetal Id.: 14
	STERNEBRA (E),	MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT
Fetal Position: RIBS (Skeletal)	Right 10	Unique Fetal Id.: 15
	RIB (S), BENT,	SLIGHT TO MODERATE - VARIATION; LEFT 3-6, 11 AND 12; RIGHT 6-12
STERNUM (Skeletal)		STERNEBRA (E), 5-6, UNOSSFIED - VARIATION; 5 ONLY

Animal: 469

Fetal Position: STERNUM (Skeletal)	Left 01	Unique Fetal Id.: 1
	STERNEBRA (E),	MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT
Fetal Position: STERNUM (Skeletal)	Left 03	Unique Fetal Id.: 3
	STERNEBRA (E),	MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 10 MG BASE/KG/DAY

Animal: 469 (CONT.)

Fetal Position: Right 01 Unique Fetal Id.: 5  
 STERNUM (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

HEAD (External) TOP, CENTER, HEMATOMA - VARIATION

Animal: 472

Fetal Position: Left 06 Unique Fetal Id.: 6  
 STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT  
 STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Right 03 Unique Fetal Id.: 12  
 STERNUM (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 AND 6

Fetal Position: Right 05 Unique Fetal Id.: 14  
 STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

Animal: 482

Fetal Position: Left 08 Unique Fetal Id.: 8  
 STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 10 MG BASE/KG/DAY

Animal: 486

Fetal Position: Left 02 Unique Fetal Id.: 2  
STERNUM  
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

Fetal Position: Left 04 Unique Fetal Id.: 4  
RIBS  
(Skeletal) RIB(S), BENT, SLIGHT TO MODERATE - VARIATION; LEFT 11; RIGHT 9,10 AND 11; SLIGHT

STERNUM  
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Right 02 Unique Fetal Id.: 11

RIBS  
(Skeletal) RIB(S), BENT, SLIGHT TO MODERATE - VARIATION; RIGHT 10 AND 11, SLIGHT 7TH  
CERVICAL RIB, PRESENT - VARIATION; LEFT

STERNUM  
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

Fetal Position: Right 06 Unique Fetal Id.: 15

RIBS  
(Skeletal) RIB(S), BENT, SLIGHT TO MODERATE - VARIATION; RIGHT 9, SLIGHT

Animal: 494

Fetal Position: Left 04 Unique Fetal Id.: 4  
SKULL  
(Skeletal) PARIETAL(S), REDUCED OSSIFICATION - VARIATION; LEFT, SLIGHT

Fetal Position: Right 01 Unique Fetal Id.: 8  
SKULL  
(Skeletal) SUPRAOCCIPITAL, REDUCED OSSIFICATION - VARIATION; SLIGHT SQUAMOSAL(S), REDUCED  
OSSIFICATION - VARIATION; LEFT, SLIGHT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 10 MG BASE/KG/DAY

Animal: 494 (CONT.)

Fetal Position: Right 03 Unique Fetal Id.: 10  
STERNUM  
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

SKULL (Skeletal) PARIETAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SLIGHT

Animal: 502

Fetal Position: Left 03 Unique Fetal Id.: 3  
STERNUM  
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

Fetal Position: Right 02 Unique Fetal Id.: 5  
STERNUM  
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Right 04 Unique Fetal Id.: 7  
STERNUM  
(Skeletal) STERNEBRA(E), 1-4, UNOSSIFIED - VARIATION; 4 ONLY STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Right 06 Unique Fetal Id.: 9  
RIBS (Skeletal) RIB(S), BENT, SLIGHT TO MODERATE - VARIATION; RIGHT 12, SLIGHT

SKULL (Skeletal) HYOID, UNOSSIFIED - VARIATION

Fetal Position: Right 08 Unique Fetal Id.: 11  
RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; BILATERAL

STERNUM  
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY

SKULL (Skeletal) SUPRAOCCIPITAL, REDUCED OSSIFICATION - VARIATION; SLIGHT

APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 30 MG BASE/KG/DAY

---

NOTE: THE FETUSES FROM LITTERS 400, 424, AND 425 SCHEDULED FOR SKELETAL EXAMINATION DISARTICULATED DURING PROCESSING. INDIVIDUAL FETAL SKELETAL EXAMINATIONS WERE NOT POSSIBLE.

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 30 MG BASE/KG/DAY

Animal: 354

Fetal Position: STERNUM (Skeletal)	Left 04	Unique Fetal Id.: 4
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT
Fetal Position: STERNUM (Skeletal)	Left 06	Unique Fetal Id.: 6
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY
Fetal Position: STERNUM (Skeletal)	Left 08	Unique Fetal Id.: 8
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5
Fetal Position: STERNUM (Skeletal)	Right 01	Unique Fetal Id.: 12
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 03	Unique Fetal Id.: 14
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT

Animal: 356

Fetal Position: STERNUM (Skeletal)	Left 02	Unique Fetal Id.: 2
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT
Fetal Position: STERNUM (Skeletal)	Left 06	Unique Fetal Id.: 6
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 30 MG BASE/KG/DAY

Animal: 370

Fetal Position: STERNUM (Skeletal)	Left 02	Unique Fetal Id.: 2
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 03	Unique Fetal Id.: 8
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 05	Unique Fetal Id.: 10
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

VERTEBRAL COLUMN  
(Skeletal)

CERVICAL ARCHES, REDUCED OSSIFICATION - VARIATION; RIGHT 3-6

Animal: 374

Fetal Position: STERNUM (Skeletal)	Left 02	Unique Fetal Id.: 2
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT
Fetal Position: STERNUM (Skeletal)	Left 04	Unique Fetal Id.: 4
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT
Fetal Position: STERNUM (Skeletal)	Left 07	Unique Fetal Id.: 7
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 30 MG BASE/KG/DAY

Animal: 374 (CONT.)

Fetal Position: Right 01 \* Unique Fetal Id.: 8

Comments: UMBILICAL HERNIA NOT EVIDENT INTERNALLY

TORSO

(External)

UMBILICUS, UMBILICAL HERNIA - NOT TABULATED SINCE IT WAS NOT CONFIRMED INTERNALLY

ABDOMEN

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; LEFT, SLIGHT

Fetal Position:  
BACK

Right 07

Unique Fetal Id.: 14

(External)

POSTERIOR, LEFT, HEMATOMA - VARIATION

Animal: 379

Fetal Position:  
ABDOMEN

Right 02

Unique Fetal Id.: 2

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT

Animal: 382

Fetal Position:  
STERNUM

Left 04

Unique Fetal Id.: 4

(Skeletal)

STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY

Fetal Position:  
SKULL

Left 06

Unique Fetal Id.: 6

(Skeletal)

HYOID, UNOSSIFIED - VARIATION

Fetal Position:  
STERNUM

Right 03

Unique Fetal Id.: 10

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2,3 AND 4

Fetal Position:  
STERNUM

Right 05

Unique Fetal Id.: 12

(Skeletal)

STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 30 MG BASE/KG/DAY

Animal: 385

Fetal Position: Right 01 Unique Fetal Id.: 6  
ABDOMEN  
(Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, SLIGHT

Animal: 399

Fetal Position: Left 01 Unique Fetal Id.: 1  
STERNUM  
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT

Fetal Position: Left 03 Unique Fetal Id.: 3  
STERNUM  
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

Fetal Position: Right 02 Unique Fetal Id.: 5  
STERNUM  
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT

Animal: 404

Fetal Position: Left 02 Unique Fetal Id.: 2  
RIBS  
(Skeletal) RIB 13, RUDDIMENTARY - VARIATION; LEFT

Fetal Position: Right 03 Unique Fetal Id.: 7  
RIBS  
(Skeletal) RIB 13, RUDDIMENTARY - VARIATION; LEFT

STERNUM  
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, SLIGHT

Fetal Position: Right 05 Unique Fetal Id.: 9  
STERNUM  
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 30 MG BASE/KG/DAY

Animal: 410

Fetal Position: ABDOMEN (Visceral)	Left 05	Unique Fetal Id.: 5
	URETER(S), HYDROURETER - VARIATION; BILATERAL, SLIGHT	
Fetal Position: ABDOMEN (Visceral)	Left 07	Unique Fetal Id.: 7
	KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT URETER(S), HYDROURETER - VARIATION; BILATERAL, SLIGHT	
Fetal Position: ABDOMEN (Visceral)	Right 04	Unique Fetal Id.: 11
	KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL	
Fetal Position: ABDOMEN (Visceral)	Right 10	Unique Fetal Id.: 17
	KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, SLIGHT	

Animal: 440

Fetal Position: STERNUM (Skeletal)	Left 02	Unique Fetal Id.: 2
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT	
Fetal Position: STERNUM (Skeletal)	Right 01	Unique Fetal Id.: 5
	STERNEBRA(E), 5-6, UNOSSFIED - VARIATION; 5 ONLY	
Fetal Position: STERNUM (Skeletal)	Right 04	Unique Fetal Id.: 8
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT	



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 30 MG BASE/KG/DAY

Animal: 441

Fetal Position: STERNUM (Skeletal)	Left 01	Unique Fetal Id.: 1
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5
Fetal Position: STERNUM (Skeletal)	Left 03	Unique Fetal Id.: 3
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM (Skeletal)	Left 07	Unique Fetal Id.: 7
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 02	Unique Fetal Id.: 9
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM (Skeletal)	Right 04	Unique Fetal Id.: 11
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 06	Unique Fetal Id.: 13
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 30 MG BASE/KG/DAY

Animal: 444

Fetal Position: STERNUM (Skeletal)	Left 02	Unique Fetal Id.: 2
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT
Fetal Position: ABDOMEN (Visceral)	Right 01	Unique Fetal Id.: 5
		KIDNEY(S), HYDRONEPHROSIS - VARIATION; LEFT, SLIGHT
Fetal Position: SKULL (Skeletal)	Right 03	Unique Fetal Id.: 7
		SUPRAOCCIPITAL, REDUCED OSSIFICATION - VARIATION; SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 05	Unique Fetal Id.: 9
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, SLIGHT

Animal: 448

Fetal Position: STERNUM (Skeletal)	Left 02	Unique Fetal Id.: 2
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, MALALIGNED
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: RIBS (Skeletal)	Left 04	Unique Fetal Id.: 4
		RIB 13, RUDIMENTARY - VARIATION; BILATERAL
Fetal Position: STERNUM (Skeletal)		Unique Fetal Id.: 5
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 30 MG BASE/KG/DAY

Animal: 448 (CONT.)

Fetal Position: Left 05 \* Unique Fetal Id.: 5

WHOLE BODY (External) WHOLE BODY, SMALL IN SIZE - NOT TABULATED, GENERAL OBSERVATION

Fetal Position: Left 06 Unique Fetal Id.: 6  
STERNUM (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Left 08 Unique Fetal Id.: 8  
STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

Fetal Position: Right 02 Unique Fetal Id.: 12

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Animal: 450

Fetal Position: Left 04 Unique Fetal Id.: 4

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Left 05 \* Unique Fetal Id.: 5

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT MICROSTOMIA

HEAD (External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT MOUTH, MICROSTOMIA - MALFORMATION JAW, AGNATHIA - MALFORMATION, TONGUE ABSENT, MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 30 MG BASE/KG/DAY

Animal: 450 (CONT.)

Fetal Position:	Left 07	Unique Fetal Id.: 7
ABDOMEN		
(Visceral)		
	KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, SLIGHT URETER(S), HYDROURETER - VARIATION; RIGHT, SLIGHT	

Fetal Position:	Left 08	Unique Fetal Id.: 8
STERNUM		
(Skeletal)		
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	

Fetal Position:	Right 01	Unique Fetal Id.: 10
STERNUM		
(Skeletal)		
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	

Fetal Position:	Right 03	Unique Fetal Id.: 12
STERNUM		
(Skeletal)		
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT	

Fetal Position:	Right 05	Unique Fetal Id.: 14
STERNUM		
(Skeletal)		
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, SLIGHT	

Animal: 460

Fetal Position:	Left 02	Unique Fetal Id.: 2
STERNUM		
(Skeletal)		
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT	

Fetal Position:	Right 04	Unique Fetal Id.: 9
RIBS		
(Skeletal)		
	RIB 13, RUDIMENTARY - VARIATION; RIGHT	

STERNUM		
(Skeletal)		
	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT	



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 30 MG BASE/KG/DAY

Animal: 475

Fetal Position: STERNUM	Left 03	Unique Fetal Id.: 3
(Skeletal)	STERNEBRA (E),	MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT
Fetal Position: STERNUM	Left 05	Unique Fetal Id.: 5
(Skeletal)	STERNEBRA (E),	MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, MALALIGNED
	STERNEBRA (E),	5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position:	Right 07 *	Unique Fetal Id.: 12

ANUS

(External) ANAL OPENING, SMALL IN SIZE - MALFORMATION

TAIL

(External) TAIL, THREAD-LIKE - MALFORMATION

Fetal Position: STERNUM	Right 10	Unique Fetal Id.: 15
(Skeletal)	STERNEBRA (E),	5-6, UNOSSIFIED - VARIATION; 5 ONLY

Animal: 483

Fetal Position: STERNUM	Left 01	Unique Fetal Id.: 1
(Skeletal)	STERNEBRA (E),	MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT
Fetal Position: STERNUM	Left 03	Unique Fetal Id.: 3
(Skeletal)	STERNEBRA (E),	MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 30 MG BASE/KG/DAY

Animal: 483 (CONT.)

Fetal Position: STERNUM (Skeletal)	Left 07	Unique Fetal Id.: 7
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT
Fetal Position: STERNUM (Skeletal)	Right 01	Unique Fetal Id.: 9
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

Fetal Position: STERNUM (Skeletal)	Right 03	Unique Fetal Id.: 11
		STERNEBRA(E), 1-4, UNOSSIFIED - VARIATION; 4 ONLY STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 AND 6

Fetal Position: STERNUM (Skeletal)	Right 05	Unique Fetal Id.: 13
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

Animal: 490

Fetal Position:	Left 01 *	Unique Fetal Id.: 1
Comments: HEMATOMA RT. PINNA NOT EVIDENT AT BOVINS (Visceral) EXAM		

HEAD

(External) PINNA(E), RIGHT, HEMATOMA - VARIATION

Fetal Position: PELVIS (Skeletal)	Right 01	Unique Fetal Id.: 7
---	----------	---------------------

PUBIS, UNOSSIFIED - VARIATION; BILATERAL

STERNUM  
(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT  
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: STERNUM (Skeletal)	Right 03	Unique Fetal Id.: 9
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 30 MG BASE/KG/DAY

Animal: 491

Fetal Position: STERNUM (Skeletal)	Left 01	Unique Fetal Id.: 1
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3,4 AND 5, SLIGHT
Fetal Position: STERNUM (Skeletal)	Left 03	Unique Fetal Id.: 3
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT
Fetal Position: ABDOMEN (Visceral)	Left 06	Unique Fetal Id.: 6
		KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT

Animal: 492

Fetal Position: STERNUM (Skeletal)	Left 02	Unique Fetal Id.: 2
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM (Skeletal)	Left 04	Unique Fetal Id.: 4
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3,4 AND 5, SLIGHT
Fetal Position: STERNUM (Skeletal)	Left 06	Unique Fetal Id.: 6
		STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
Fetal Position: STERNUM (Skeletal)	Right 03	Unique Fetal Id.: 11
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 30 MG BASE/KG/DAY

Animal: 503

Fetal Position: STERNUM	Left 07	Unique Fetal Id.: 7
(Skeletal)		STERNEBRA (E), 1-4, UNOSSFIED - VARIATION; 4 ONLY STERNEBRA (E), 5-6, UNOSSFIED - VARIATION; 5 AND 6
Fetal Position: STERNUM	Right 02	Unique Fetal Id.: 11
(Skeletal)		STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

NOTE: THE FETUSES FROM LITTERS 385, 392, 410, AND 417 SCHEDULED FOR SKELETAL EXAMINATION DISARTICULATED DURING PROCESSING. INDIVIDUAL FETAL SKELETAL EXAMINATIONS WERE NOT POSSIBLE.



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 353

Fetal Position: Left 02 Unique Fetal Id.: 2

RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; RIGHT

STERNUM (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SQUAMOSAL(S), UNOSSIFIED - VARIATION; BILATERAL

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Left 03 \* Unique Fetal Id.: 3

Comments: EXTERNALS NOT CONFIRMED VISCERALLY

HEAD (External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 4 PRESENT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 353 (CONT.)

Unique Fetal Id.: 4

Fetal Position: Left 04

RIBS (Skeletal) RIB 14, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL

HEAD (External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Left 05 \* Unique Fetal Id.: 5

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

EYES (External) EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; RIGHT MICROPHTHALMIA

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 353 (CONT.)

Fetal Position:	Left 06	Unique Fetal Id.: 6
RIBS	(Skeletal)	RIB 14, RUDIMENTARY - VARIATION; BILATERAL

STERNUM	(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT
---------	------------	--

VERTEBRAL COLUMN	(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
------------------	------------	---

SKULL	(Skeletal)	SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL
-------	------------	---

HEAD	(External)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED MOUTH, MACROSTOMIA - MALFORMATION
------	------------	--

Fetal Position:	Left 07 *	Unique Fetal Id.: 7
-----------------	-----------	---------------------

Comments: EXTERNALS CONFIRMED VISCERALLY

HEAD	(External)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, MALPOSITIONED MOUTH, MACROSTOMIA - MALFORMATION
------	------------	---

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 353 (CONT.)

Fetal Position: Left 08 Unique Fetal Id.: 8

RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; BILATERAL

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2,3 AND 4, SLIGHT STERNEBRA(E), 1-4, UNOSSIFIED - VARIATION; 2 ONLY

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL

HEAD (External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 4 PRESENT MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Right 02 \* Unique Fetal Id.: 10

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

HEAD (External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 4 PRESENT MOUTH, MACROSTOMIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 353 (CONT.)

Fetal Position:	Right 03	Unique Fetal Id.: 11
RIBS	(Skeletal)	RIB 14, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL

STERNUM	(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY
---------	------------	---

VERTEBRAL COLUMN	(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
------------------	------------	---

SKULL	(Skeletal)	SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL
-------	------------	---

HEAD	(External)	FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION
------	------------	--

Fetal Position:	Right 04 *	Unique Fetal Id.: 12
-----------------	------------	----------------------

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

HEAD	(External)	FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION
------	------------	--

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 353 (CONT.)

Fetal Position:	Right 05	Unique Fetal Id.: 13
RIBS (Skeletal)	RIB 14, RUDIMENTARY - VARIATION; BILATERAL	
STERNUM (Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT	
VERTEBRAL COLUMN (Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
SKULL (Skeletal)	SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL	
HEAD (External)	FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION	

Animal: 362

Fetal Position:	Left 03 *	Unique Fetal Id.: 3
Comments:	EXTERNALS CONFIRMED EXCEPT FACIAL PAPILLAE--SUPERNUMERARY	
EYES (External)	EYELID(S), OPEN EYELID(S) - MALFORMATION; LEFT	
ABDOMEN (Visceral)	KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT URETER(S), HYDROURETER - VARIATION; BILATERAL, SLIGHT	
HEAD (External)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, PALATE, CLEFT PALATE - MALFORMATION	

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 362 (CONT.)

Fetal Position: Left 04 Unique Fetal Id.: 4  
RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; BILATERAL

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: PORTION OF FRONTALS, PARIETALS BILATERAL--ABSENT; MAXILLAE MICROGNATHIA: MAXILLAE AND PREMAXILLAE BILATERAL--SMALL IN SIZE

EYES (External) EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

Fetal Position: Left 05 \* Unique Fetal Id.: 5

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

EYES (External) EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

ABDOMEN (Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT URETER(S), HYDROURETER - VARIATION; BILATERAL, SLIGHT

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, ABSENT; RIGHT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, ENCEPHALOCELE - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 362 (CONT.)

Fetal Position: Left 06 Unique Fetal Id.: 6

RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; RIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: PORTION OF INTERPARIETAL, FRONTALS, PARIETALS BILATERAL--ABSENT; CLEFT PALATE SUPRAOCCIPITAL, REDUCED OSSIFICATION - VARIATION MAXILLA(E), SMALL IN SIZE - MALFORMATION PREMAXILLA(E), SMALL IN SIZE - CONFIRMATION

EYES (External) EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

Fetal Position: Left 07 \* Unique Fetal Id.: 7

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

ABDOMEN (Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT URETER(S), HYDROURETER - VARIATION; BILATERAL, SLIGHT

HEAD (External) HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, ABSENT; RIGHT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, HYDROCEPHALY - MALFORMATION; BILATERAL, SEVERE MOUTH, MACROSTOMIA - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 362 (CONT.)

Unique Fetal Id.: 8

Fetal Position: Left 08

RIBS

(Skeletal)

RIB 14, RUDIMENTARY - VARIATION; LEFT

STERNUM

(Skeletal)

STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; RIGHT THORACIC ARCHES 13 AND 14--FUSED; THORACIC CENTRUM 12--BIPARTITE AND ENLARGED ON RIGHT SIDE; THORACIC CENTRUM 13--FORMED ON LEFT SIDE ONLY; THORACIC CENTRUM 14 ENLARGED ON RIGHT SIDE

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: PORTION OF FRONTALS, PARIETALS BILATERAL, INTERPARIETAL--ABSENT; MAXILLAE MICROGNATHIA: MAXILLAE, PREMAXILLAE BILATERAL--SMALL IN SIZE; CLEFT PALATE SUPRAOCCIPITAL, REDUCED OSSIFICATION - VARIATION

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD

(External)

PINNA (E), PINNA (E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED

Comments: FACIAL PAPILLA (E), FACIAL PAPILLA (E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 362 (CONT.)

Fetal Position: Right 01 \*

Unique Fetal Id.: 10

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

ABDOMEN

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT URETER(S), HYDROURETER  
- VARIATION; BILATERAL, SLIGHT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, ABSENT FACIAL PAPILLA(E),  
FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, ENCEPHALOCELE -  
MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, PALATE, CLEFT PALATE -  
MALFORMATION

(Visceral)

PALATE, CLEFT PALATE - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 362 (CONT.)

Fetal Position:	Right 02	Unique Fetal Id.: 11
STERNUM	(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT

VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE/RIBS, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; RIGHT THORACIC ARCHES 12-17--FUSED; RIGHT RIB 13--ABSENT; THORACIC CENTRA 10-14 AND LUMBAR CENTRA 1-3--MALFORMED (FUSED, BIPARTITE, MALALIGNED AND/OR HEMICENTRA)

SKULL  
(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EX: PORTION OF FRONTALS, PARIETALS BILATERAL--SMALL IN SIZE; MAXILLAE MICROGNATHIA: MAXILLAE, PREMAXILLAE BILATERAL--SMALL IN SIZE; BILATERAL MICROPTHALMIA: BONES FORMING EYE SOCKETS MALFORMED SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL

EYES  
(External)

EYE(S), ANOPHTHALMIA/MICROPTHALMIA - MALFORMATION; BILATERAL MICROPTHALMIA EYELID(S), OPEN EYELID(S) - MALFORMATION; LEFT

HEAD  
(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED

Comments: FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 362 (CONT.)

Fetal Position: Right 04 \* Unique Fetal Id.: 13

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

### HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Right 05  
STERNUM

Unique Fetal Id.: 14

(Skeletal)

STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: PORTIONS OF FRONTALS, PARIETALS BILATERAL--ABSENT; MAXILLAE MICROGNATHIA: MAXILLAE, PREMAXILLAE BILATERAL--SMALL IN SIZE; CLEFT PALATE SUPRAOCCIPITAL, REDUCED OSSIFICATION - VARIATION INTERPARIETAL, UNOSSIFIED - VARIATION

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL MICROPHTHALMIA

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 362 (CONT.)

Fetal Position: Right 06 \*

Unique Fetal Id.: 15

Comments: EXTERNALS CONFIRMED VISCERALLY

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED BRAIN, EXENCEPHALY - MALFORMATION  
(Visceral) BRAIN, HYDROCEPHALY - MALFORMATION; BILATERAL, MODERATE

Animal: 364

Fetal Position: Left 01 \*

Unique Fetal Id.: 1

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

ABDOMEN

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT URETER(S), HYDROURETER - VARIATION; BILATERAL, SLIGHT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 364 (CONT.)

Unique Fetal Id.: 2

Left 02

Fetal Position:  
VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; LEFT LUMBAR ARCH 3--SMALL, MALFORMED AND FUSED TO LEFT LUMBAR ARCH 4; LUMBAR CENTRUM 3 FORMED ON RIGHT SIDE ONLY; LUMBAR CENTRUM 2 ENLARGED ON LEFT SIDE; LUMBAR CENTRUM 4 MALALIGNED

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: PARIETALS BILATERAL--MALFORMED MAXILLA(E), MALFORMED - MALFORMATION; BILATERAL PREMAXILLA(E), MALFORMED - MALFORMATION; BILATERAL SQUAMOSAL(S), UNOSSIFIED - VARIATION; BILATERAL

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION

Fetal Position:

Left 04 \*

Unique Fetal Id.: 4

Comments: EXTERNALS CONFIRMED VISCERALLY

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT ANOPHTHALMIA; RIGHT MICROPHTHALMIA

ABDOMEN

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, MODERATE URETER(S), HYDROURETER - VARIATION; BILATERAL, MODERATE

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 364 (CONT.)

Fetal Position: Left 05

Unique Fetal Id.: 5

STERNUM  
(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT

VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: PORTIONS OF FRONTALS, PARIETALS BILATERAL--ABSENT; MAXILLAE MICROGNATHIA: MAXILLAE AND PREMAXILLAE BILATERAL--SMALL AND MALFORMED SUPRAOCCIPITAL, REDUCED OSSIFICATION - VARIATION SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

Fetal Position: Right 02 \*

Unique Fetal Id.: 7

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL

PAPILLAE--MALPOSITIONED OR ABSENT

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

ABDOMEN

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, SLIGHT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 364 (CONT.)

Fetal Position:	Right 03	Unique Fetal Id.: 8
RIBS		
(Skeletal)	RIB 14, RUDIMENTARY - VARIATION; BILATERAL	

VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; LEFT THORACIC ARCHES 12 AND 13--FUSED; THORACIC CENTRA 12 AND 13--BIPARTITE AND FUSED/ENLARGED ON RIGHT SIDE

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: INTERPARIETAL, PORTION OF FRONTALS, PARIETALS BILATERAL--ABSENT; MAXILLAE MICROGNATHIA: PREMAXILLAE AND MAXILLAE BILATERAL--MALFORMED AND SMALL; BILATERAL ANOPHTHALMIA: EYE SOCKETS--MALFORMED; CLEFT PALATE SUPRAOCCIPITAL, REDUCED OSSIFICATION - VARIATION

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED BRAIN, EXENCEPHALY - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION



APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 364 (CONT.)

Fetal Position: Right 05 \*

Unique Fetal Id.: 10

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED OR ABSENT

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT MICROPHTHALMIA  
EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

ABDOMEN

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND  
MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION;  
MALPOSITIONED OR ABSENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA -  
MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, TONGUE,  
MACROGLOSSIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 364 (CONT.)

Fetal Position: Right 06 Unique Fetal Id.: 11

RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; BILATERAL

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: INTERPARIETAL, PORTION OF FRONTALS, PARIETALS BILATERAL--ABSENT; MAXILLAE MICROGNATHIA: MAXILLAE AND PREMAXILLAE BILATERAL--MALFORMED AND SMALL; CLEFT PALATE SQUAMOSAL(S), UNOSSIFIED - VARIATION; BILATERAL

EYES (External) EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 364 (CONT.)

Fetal Position: Right 08 \*

Unique Fetal Id.: 13

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED OR ABSENT

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

### ABDOMEN

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

Animal: 366

Fetal Position: Left 01 \*

Unique Fetal Id.: 1

Comments: EXTERNALS CONFIRMED AT VISCERAL EXAM EXCEPT FACIAL PAPILLAE ABSENT

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT MICROPHTHALMIA

### ABDOMEN

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT URETER(S), HYDROURETER - VARIATION; BILATERAL, SLIGHT

### HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

(Visceral)

BRAIN, HYDROCEPHALY - MALFORMATION; BILATERAL, SLIGHT

(External)

MOUTH, MACROSTOMIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 366 (CONT.)

Fetal Position: Left 02

Unique Fetal Id.: 2

RIBS (Skeletal)

RIB 14, RUDIMENTARY - VARIATION; BILATERAL

STERNUM (Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2,3 AND 4, SLIGHT  
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

SKULL (Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; LEFT MICROPTHALMIA: LEFT  
EYE SOCKET--SMALL SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL  
TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

EYES (External)

EYE(S), ANOPHTHALMIA/MICROPTHALMIA - MALFORMATION; LEFT MICROPTHALMIA

HEAD (External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR  
ABSENT

Fetal Position: Left 03 \*

Unique Fetal Id.: 3

Comments: EXTERNALS NOT CONFIRMED VISCERALLY

HEAD (External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 4  
PRESENT

Fetal Position: Left 04

Unique Fetal Id.: 4

RIBS (Skeletal)

RIB 14, RUDIMENTARY - VARIATION; BILATERAL

STERNUM (Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2,3 AND 4, SLIGHT  
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

SKULL (Skeletal)

TYMPANIC RING(S), ABSENT - MALFORMATION; LEFT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 366 (CONT.)

Fetal Position: Left 05 \* Unique Fetal Id.: 5

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED AND ABSENT

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT MICROPHTHALMIA

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; RIGHT, MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT OR MALPOSITIONED, ONLY 4 PRESENT

Fetal Position: Left 06

Unique Fetal Id.: 6

### RIBS

(Skeletal)

RIB 14, RUDIMENTARY - VARIATION; BILATERAL

### VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; LEFT MICROPHTHALMIA: LEFT EYE SOCKET--SMALL TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT MICROPHTHALMIA

### HEAD

(External)

MOUTH, MICROSTOMIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 366 (CONT.)

Fetal Position: Left 07 \* Unique Fetal Id.: 7

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

EYES (External) EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT MICROPHTHALMIA

HEAD (External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Left 08 \* Unique Fetal Id.: 8

Comments: LEFT ANOPHTHALMIA COULD NOT BE CONFIRMED SKELETALLY

RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; BILATERAL (FROM A 15TH SET OF THORACIC VERTEBRAE)

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

VERTEBRAL COLUMN (Skeletal) VERTEBRAE/RIBS, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; 14 THORACIC VERTEBRAE; RIGHT RIBS 7 AND 8--FUSED AT PROXIMAL END; LEFT RIBS 11 AND 12--FUSED AT PROXIMAL END AND 1/3 OF RIB LENGTH; LEFT RIB 7--ARTICULATING FROM 2 VERTEBRAE; SOME ASSOCIATED VERTEBRAE--FUSED, SMALL AND/OR MALFORMED

SKULL (Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: FRONTALS AND PARIETALS BILATERAL--SMALL TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

EYES (External) EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT ANOPHTHALMIA EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT BRAIN, EXENCEPHALY - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 366 (CONT.)

Fetal Position: Left 12 \* Unique Fetal Id.: 12

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED AND ABSENT

### HEAD

(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, SMALL IN SIZE FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT AND MALPOSITIONED

Fetal Position: Right 02 \* Unique Fetal Id.: 14

Comments: LEFT MICROPTHALMIA NOT CONFIRMED

### STERNUM

(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

### SKULL

(Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: FRONTALS AND PARIETALS BILATERAL--SMALL; RIGHT MICROPTHALMIA: EYE SOCKET--SMALL TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

### EYES

(External) EYE(S), ANOPHTHALMIA/MICROPTHALMIA - MALFORMATION; BILATERAL MICROPTHALMIA

### HEAD

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 4 PRESENT BRAIN, EXENCEPHALY - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 368

Fetal Position: Left 01 \* Unique Fetal Id.: 1

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT MICROPHTHALMIA; RIGHT ANOPHTHALMIA

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED MOUTH, MACROSTOMIA - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION

Fetal Position: Left 02  
STERNUM

Unique Fetal Id.: 2

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2,3 AND 4, SLIGHT  
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

### SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; DOMED HEAD AND EXENCEPHALY: FRONTALS AND PARIETALS BILATERAL--SMALL IN SIZE; BILATERAL ANOPHTHALMIA: EYE SOCKETS--SMALL IN SIZE; MAXILLAE MICROGNATHIA: MAXILLAE AND PREMAXILLAE BILATERAL--SMALL AND MALFORMED; CLEFT PALATE

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

### HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 368 (CONT.)

Fetal Position: Left 03 \* Unique Fetal Id.: 3

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED

EYES

(External) EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

HEAD

(External) HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED MOUTH, MACROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

Fetal Position: Left 04

Unique Fetal Id.: 4

STERNUM

(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3,4 AND 5, SLIGHT

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal) TYMPANIC RING(S), UNOSSIFIED - VARIATION; RIGHT

HEAD

(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; RIGHT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position: Left 05 \*

Unique Fetal Id.: 5

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

HEAD

(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 368 (CONT.)

Fetal Position: Left 06 Unique Fetal Id.: 6

RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; RIGHT

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: PORTIONS OF INTERPARIETAL, FRONTALS/PARIETALS BILATERAL--ABSENT; MAXILLAE MICROGNATHIA: MAXILLAE AND PREMAXILLAE BILATERAL--SMALL AND MALFORMED TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

EYES (External) EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

Fetal Position: Left 07 \* Unique Fetal Id.: 7

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED OR ABSENT

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 368 (CONT.)

Unique Fetal Id.: 8

Fetal Position: Left 08

RIBS

(Skeletal)

RIB 14, RUDIMENTARY - VARIATION; LEFT

VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; LEFT MICROPHTHALMIA: LEFT EYE SOCKET--SMALL SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), ABSENT - MALFORMATION; RIGHT

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT MICROPHTHALMIA

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT

Fetal Position: Right 01 \*

Unique Fetal Id.: 9

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED OR ABSENT

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; RIGHT MICROPHTHALMIA EYELID(S), OPEN EYELID(S) - MALFORMATION; LEFT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT BRAIN, ENCEPHALOCELE - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 368 (CONT.)

Fetal Position: Right 02 Unique Fetal Id.: 10

RIBS (Skeletal) RIB 14, FULL - VARIATION; BILATERAL

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2,3 AND 4, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, ABSENT FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT

Fetal Position: Right 03 \* Unique Fetal Id.: 11

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED

EYES (External) EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT MICROPHTHALMIA

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 368 (CONT.)

Fetal Position: Right 04 Unique Fetal Id.: 12  
 STERNUM  
 (Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, SLIGHT

VERTEBRAL COLUMN  
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal)  
 SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; LEFT MICROPHTHALMIA: EYE SOCKET--SMALL; CLEFT PALATE SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

EYES (External)  
 EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT MICROPHTHALMIA EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

HEAD (External)  
 PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT MOUTH, PALATE, CLEFT PALATE - MALFORMATION

Fetal Position: Right 06 Unique Fetal Id.: 14  
 VERTEBRAL COLUMN  
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal)  
 SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; CLEFT PALATE SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

HEAD (External)  
 PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 372

Fetal Position: Left 01 \*

Unique Fetal Id.: 1

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; LEFT

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Left 02

Unique Fetal Id.: 2

RIBS

(Skeletal)

7TH CERVICAL RIB, PRESENT - VARIATION; BILATERAL

STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

VERTEBRAL COLUMN

(Skeletal)

CERVICAL ARCHES, REDUCED OSSIFICATION - VARIATION; 3-6 BILATERAL

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; DOMED HEAD; BILATERAL ANOPHTHALMIA: NO EYE SOCKETS; MAXILLAE MICROGNATHIA SQUAMOSAL(S), ABSENT - MALFORMATION; BILATERAL TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 372 (CONT.)

Fetal Position: Left 03 \* Unique Fetal Id.: 3

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED OR ABSENT

EYES

(External) EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

HEAD

(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED; LEFT, SMALL IN SIZE FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT MOUTH, PALATE, CLEFT PALATE - MALFORMATION

Fetal Position: Left 04 \* Unique Fetal Id.: 4

SKULL

(Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; LEFT MICROPTHALMIA: SMALL EYE SOCKET; MANDIBULAR MICROGNATHIA TYMPANIC RING(S), ABSENT - MALFORMATION

EYES

(External) EYE(S), ANOPHTHALMIA/MICROPTHALMIA - MALFORMATION; LEFT MICROPTHALMIA EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

HEAD

(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION JAW, MANDIBLE, MICROGNATHIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 372 (CONT.)

Fetal Position: Right 01 \* Unique Fetal Id.: 5

Comments: EXTERNALS CONFIRMED EXCEPT FACIAL PAPILLAE--MALPOSITIONED

EYES (External) EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL MICROPHTHALMIA

ABDOMEN (Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED

Fetal Position: Right 02 Unique Fetal Id.: 6  
STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2,3 AND 4, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; LEFT MICROPHTHALMIA: LEFT EYE SOCKET--SMALL SQUAMOSAL(S), UNOSSIFIED - VARIATION; BILATERAL TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

EYES (External) EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT MICROPHTHALMIA

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 372 (CONT.)

Fetal Position: Right 04 \* Unique Fetal Id.: 8

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

### HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED MOUTH, PALATE, CLEFT PALATE - MALFORMATION

Fetal Position: Right 05  
STERNUM (Skeletal)

Unique Fetal Id.: 9

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

VERTEBRAL COLUMN (Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; DOMED HEAD; LEFT ANOPHTHALMIA: NO LEFT EYE SOCKET; RIGHT MICROPHTHALMIA: SMALL RIGHT EYE SOCKET TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT ANOPHTHALMIA; RIGHT MICROPHTHALMIA

### HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 372 (CONT.)

Fetal Position: Right 06 \* Unique Fetal Id.: 10  
 Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SMALL OR ABSENT

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

### HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SMALL IN SIZE OR ABSENT

(Visceral)

PALATE, CLEFT PALATE - MALFORMATION; SLIGHT

Fetal Position: Right 07

Unique Fetal Id.: 11

### STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT

### VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; RIGHT LUMBAR ARCHES 2 AND 3--FUSED; RIGHT SIDES OF THORACIC CENTRUM 13 AND LUMBAR CENTRUM 1--FUSED

### SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; LEFT MICROPHTHALMIA: LEFT EYE SOCKET--SMALL TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT MICROPHTHALMIA

### HEAD

(External)

HEAD, HEMATOMA - VARIATION; HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 372 (CONT.)

Fetal Position: Right 08 \*

Unique Fetal Id.: 12

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED OR ABSENT

### ABDOMEN

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT

Fetal Position: Right 09  
STERNUM (Skeletal)

Unique Fetal Id.: 13

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

VERTEBRAL COLUMN (Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE/RIBS, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; RIGHT THORACIC ARCH 13--SMALL; ARTICULATING HEAD OF RIGHT RIB 13--SMALL AND ROUNDED; THORACIC CENTRUM 12--MALALIGNED

### SKULL

(Skeletal)

SQUAMOSAL(S), UNOSSIFIED - VARIATION; BILATERAL TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

### EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; LEFT

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED MOUTH, MACROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 389

Fetal Position: Left 01  
EYES

Unique Fetal Id.: 1

(External) EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT ANOPHTHALMIA

HEAD

(External) HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Left 02 \*

Unique Fetal Id.: 2

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; RIGHT MICROPHTHALMIA EYELID(S), OPEN EYELID(S) - MALFORMATION; LEFT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; RIGHT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT AND MALPOSITIONED BRAIN, ENCEPHALOCELE - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Right 01  
EYES

Unique Fetal Id.: 3

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL MICROPHTHALMIA

HEAD

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION; BILATERAL JAW, MAXILLAE, MICROGNATHIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 389 (CONT.)

Fetal Position: Right 02 \*

Unique Fetal Id.: 4

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED OR ABSENT

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT MICROPHTHALMIA

ABDOMEN

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT URETER(S), HYDROURETER - VARIATION; BILATERAL, SLIGHT

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT AND MALPOSITIONED PALATE, CLEFT PALATE - MALFORMATION; SEVERE

Fetal Position: Right 03

Unique Fetal Id.: 5

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, NONE PRESENT BRAIN, ENCEPHALOCELE - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION JAW, MANDIBLE, MICROGNATHIA - MALFORMATION JAW, RIGHT MANDIBLE, NUMEROUS CLEFTS - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 389 (CONT.)

Fetal Position: Right 04 \* Unique Fetal Id.: 6

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

EYES (External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL MICROPHTHALMIA

ABDOMEN

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT URETER(S), HYDROURETER  
- VARIATION; BILATERAL, SLIGHT

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION;  
BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E)  
ANOMALY - MALFORMATION; ABSENT MOUTH, MACROSTOMIA - MALFORMATION JAW, MAXILLAE,  
MICROGNATHIA - MALFORMATION  
PALATE, CLEFT PALATE - MALFORMATION; SLIGHT

(Visceral)

Animal: 391

Fetal Position: Left 01 Unique Fetal Id.: 1

HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position: Left 02 \*

Unique Fetal Id.: 2

Comments: EXTERNALS NOT CONFIRMED VISCERALLY

HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position:

Left 03

Unique Fetal Id.: 3

HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 391 (CONT.)

Fetal Position: Right 01 \* Unique Fetal Id.: 4  
Comments: EXTERNALS CONFIRMED EXCEPT FACIAL PAPILLAE--MALPOSITIONED

HEAD

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Right 02  
HEAD

Unique Fetal Id.: 5

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

Fetal Position: Right 03 \*

Unique Fetal Id.: 6

Comments: EXTERNALS NOT CONFIRMED VISCERALLY

HEAD

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

Fetal Position: Right 04  
HEAD

Unique Fetal Id.: 7

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position: Right 05 \*

Unique Fetal Id.: 8

Comments: EXTERNALS CONFIRMED EXCEPT FACIAL PAPILLAE--ABSENT

HEAD

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Right 06  
HEAD

Unique Fetal Id.: 9

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT MOUTH, MACROSTOMIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 391 (CONT.)

Fetal Position: Right 07 \* Unique Fetal Id.: 10

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

HEAD

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 4 PRESENT MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Right 08 Unique Fetal Id.: 11

HEAD

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT

Fetal Position: Right 09 \* Unique Fetal Id.: 12

Comments: EXTERNALS CONFIRMED VISCERALLY

HEAD

(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Right 10 Unique Fetal Id.: 13

HEAD

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 401

Fetal Position: Left 02 \* Unique Fetal Id.: 2

Comments: ALL TAGS AND FETUSES PRESERVED IN ALCOHOL (2, 5, 9 AND 11) WERE INADVERTENTLY SEPARATED BEFORE THE SKELETAL EXAMS AND THEN RETAGGED BASED UPON EXTERNAL OBSERVATIONS.

### RIBS

RIB 14, RUDIMENTARY - VARIATION; BILATERAL

### VERTEBRAL COLUMN (Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION; LEFT VERTEBRAE, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; LUMBAR VERTEBRA 2--HAS NO LEFT ARCH, SURROUNDING LEFT ARCHES--LARGE

### SKULL

#### (Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: LARGE GAP BETWEEN PARIETALS, INTERPARIETAL--MALFORMED; BILATERAL MICROPHthalmIA: EYE SOCKETS BILATERAL--SMALL TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

### EYES

#### (External)

EYE(S), ANOPHTHALMIA/MICROPHthalmIA - MALFORMATION; BILATERAL MICROPHthalmIA

### HEAD

#### (External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 401 (CONT.)

Fetal Position: Left 03 \* Unique Fetal Id.: 3

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL MICROPHTHALMIA EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

Fetal Position: Left 05 \* Unique Fetal Id.: 5

Comments: SEE COMMENT ON FETUS 2

### RIBS

(Skeletal)

RIB 14, FULL - VARIATION; BILATERAL

### VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; ENCEPHALOCELE: GAP BETWEEN PARIETALS AND POSTERIOR OF FRONTALS TYMPANIC RING(S), UNOSSIFIED - VARIATION; LEFT

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 4 PRESENT BRAIN, ENCEPHALOCELE - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 401 (CONT.)

Fetal Position: Right 01 \* Unique Fetal Id.: 7

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION

(Visceral)

PALATE, CLEFT PALATE - MALFORMATION; MODERATE

Fetal Position: Right 03

Unique Fetal Id.: 9

### RIBS

(Skeletal)

RIB(S), FUSED - MALFORMATION; LEFT 11 AND 12, PROXIMAL HALF RIB 14, RUDIMENTARY - VARIATION; BILATERAL

### VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: LARGE PORTIONS OF FRONTALS, PARIETALS, INTERPARIETAL AND SUPRAOCCIPITAL--ABSENT; MAXILLAE MICROGNATHIA TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

### EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 401 (CONT.)

Fetal Position: Right 04 \*

Unique Fetal Id.: 10

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

HEAD

(External)

HEAD, CEPHALOCELE - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

Fetal Position: Right 05

Unique Fetal Id.: 11

VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position: Right 06 \*

Unique Fetal Id.: 12

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION JAW, MANDIBLE, MICROGNATHIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 407

Fetal Position:	Left 01	Unique Fetal Id.: 1
HEAD		
(External)		PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT MOUTH, PALATE, CLEFT PALATE - MALFORMATION
Fetal Position:	Left 02 *	Unique Fetal Id.: 2
Comments: EXTERNALS NOT EVIDENT VISCERALLY		
HEAD		
(External)		FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY
Fetal Position:	Left 03	Unique Fetal Id.: 3
HEAD		
(External)		PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, MALFORMED; RIGHT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT
Fetal Position:	Left 04 *	Unique Fetal Id.: 4
Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY		
EYES (External)		EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL
ABDOMEN (Visceral)		KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT URETER(S), HYDROURETER - VARIATION; BILATERAL, SLIGHT
HEAD (External)		PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION
Fetal Position:	Left 05	Unique Fetal Id.: 5
HEAD (External)		PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 407 (CONT.)

Fetal Position: Right 02 \* Unique Fetal Id.: 7

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY DORSAL, HEMATOMA - VARIATION

Fetal Position: Right 03

Unique Fetal Id.: 8

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, SMALL IN SIZE AND MALPOSITIONED; RIGHT, DETACHED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position: Right 05 \* Unique Fetal Id.: 10

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED

### ABDOMEN

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT URETER(S), HYDROURETER - VARIATION; BILATERAL, SLIGHT

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Right 06

Unique Fetal Id.: 11

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT DORSAL, HEMATOMA - VARIATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 407 (CONT.)

Fetal Position: Right 07 \*

Unique Fetal Id.: 12

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

### ABDOMEN

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; MALPOSITIONED FACIAL PAPILLA(E),  
FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, PALATE, CLEFT  
PALATE - MALFORMATION

Fetal Position: Right 08

Unique Fetal Id.: 13

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL  
PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Animal: 422

Fetal Position: Left 01 \*

Unique Fetal Id.: 1

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT ANOPHTHALMIA; RIGHT  
MICROPHTHALMIA

### HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION;  
BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E)  
ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT MOUTH, PALATE, CLEFT PALATE -  
MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 422 (CONT.)

Fetal Position: Left 02 Unique Fetal Id.: 2

HEAD

(External) HEAD, DOMED HEAD - MALFORMATION FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

Fetal Position: Left 03 \* Unique Fetal Id.: 3

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

EYES

(External) EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; RIGHT ANOPHTHALMIA

HEAD

(External) HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

Fetal Position: Left 04 Unique Fetal Id.: 4

HEAD

(External) HEAD, DOMED HEAD - MALFORMATION FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

Fetal Position: Left 06 \* Unique Fetal Id.: 6

Comments: EXTERNALS NOT CONFIRMED VISCERALLY

HEAD

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 4 PRESENT

Fetal Position: Left 07 Unique Fetal Id.: 7

HEAD

(External) HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 422 (CONT.)

Fetal Position: Left 09 \*

Unique Fetal Id.: 9

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

### HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position: Left 10

Unique Fetal Id.: 10

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT ANOPHTHALMIA

### HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

Fetal Position: Right 01 \*

Unique Fetal Id.: 11

Comments: EXTERNALS NOT CONFIRMED VISCERALLY

### HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED

### Fetal Position: Right 02

HEAD

Unique Fetal Id.: 12

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 422 (CONT.)

Fetal Position: Right 03 \* Unique Fetal Id.: 13

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Right 04

HEAD

(External)

Unique Fetal Id.: 14

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED

Animal: 423

Fetal Position: Left 02

HEAD

(External)

Unique Fetal Id.: 2

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

Fetal Position: Left 03 \*

HEAD

(External)

Unique Fetal Id.: 3

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

Fetal Position: Left 04

HEAD

(External)

Unique Fetal Id.: 4

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 423 (CONT.)

Fetal Position: Left 05 \* Unique Fetal Id.: 5

Comments: EXTERNALS NOT CONFIRMED VISCERALLY

HEAD

(External)

FACIAL PAPILLA(E),  
PRESENT

FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3

Fetal Position: Left 06

HEAD

(External)

FACIAL PAPILLA(E),  
PRESENT

FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3

Fetal Position: Left 07 \*

Unique Fetal Id.: 7

Comments: EXTERNALS NOT CONFIRMED VISCERALLY

HEAD

(External)

FACIAL PAPILLA(E),

FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED

Fetal Position: Right 01

HEAD

(External)

FACIAL PAPILLA(E),  
PRESENT

FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3

Fetal Position: Right 02 \*

Unique Fetal Id.: 9

Comments: EXTERNALS NOT CONFIRMED VISCERALLY

HEAD

(External)

FACIAL PAPILLA(E),  
PRESENT

FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3

Fetal Position: Right 03

HEAD

(External)

FACIAL PAPILLA(E),  
PRESENT

FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3

APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 423 (CONT.)

Fetal Position: Right 04 \* Unique Fetal Id.: 11

Comments: EXTERNALS NOT CONFIRMED VISCERALLY

HEAD

(External)

FACIAL PAPILLA(E),  
PRESENT

FACIAL PAPILLA(E) ANOMALY -

MALFORMATION; ABSENT, ONLY 3

Fetal Position: Right 05

Unique Fetal Id.: 12

HEAD

(External)

FACIAL PAPILLA(E),  
PRESENT

FACIAL PAPILLA(E) ANOMALY -

MALFORMATION; ABSENT, ONLY 3



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 426

Fetal Position: Left 01 Unique Fetal Id.: 1

ANUS (External) ANUS, ANAL ATRESIA - MALFORMATION

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE/RIBS, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; VERTEBRAL DEFECT: LEFT LUMBAR ARCHES 2 AND 4--FUSED, SOME SURROUNDING VERTEBRAL ARCHES--MALFORMED, 3 LEFT SACRAL ARCHES--FUSED, LOWER THORACIC AND LUMBAR CENTRA--MALALIGNED, BIPARTITE AND/OR FUSED TO EACH OTHER, RIGHT RIB 13--FLOATING (ARTICULATING HEAD SMALL AND ROUNDED AND FAR FROM VERTEBRA)

SKULL (Skeletal) TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

EYES (External) EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

TAIL (External) TAIL, SHORT AND CURLY - MALFORMATION

BACK (External) BACK, APPARENT VERTEBRAL DEFECT - MALFORMATION

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MICROSTOMIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 426 (CONT.)

Fetal Position:	Left 02	Unique Fetal Id.: 2
ANUS	(External)	ANUS, ANAL ATRESIA - MALFORMATION
STERNUM	(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT
VERTEBRAL COLUMN	(Skeletal)	VERTEBRAE/RIBS, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; SEVERAL LUMBAR AND LOWER THORACIC ARCHES--FUSED; LEFT RIBS 8 AND 9 FUSED AT POINT NEAR ARTICULATING HEADS; LEFT RIB 12 ARISES 1/5 WAY DISTALLY FROM LEFT RIB 11; LEFT RIB 13--ABSENT
SKULL	(Skeletal)	SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; BILATERAL ANOPHTHALMIA: SMALL EYE SOCKETS TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL
EYES	(External)	EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA
TAIL	(External)	TAIL, ABSENT - MALFORMATION
BACK	(External)	BACK, SPINA BIFIDA - MALFORMATION
HEAD	(External)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, ABSENT; RIGHT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY DORSAL, HEMATOMA - VARIATION BRAIN, MICROCEPHALY - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 426 (CONT.)

Fetal Position: Left 03 \* Unique Fetal Id.: 3

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

EYES

(External) EYELID(S), OPEN EYELID(S) - MALFORMATION; LEFT

HEAD

(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND  
MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION;  
(Visceral) SUPERNUMERARY  
PALATE, CLEFT PALATE - MALFORMATION; SLIGHT

Fetal Position: Left 04

Unique Fetal Id.: 4

RIBS

(Skeletal) RIB 14, RUDIMENTARY - VARIATION; LEFT

STERNUM

(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; BILATERAL MACROPHTHALMIA:  
LARGE EYE SOCKETS TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

EYES

(External) EYE(S), MACROPHTHALMIA - MALFORMATION; BILATERAL EYELID(S), OPEN EYELID(S) -  
MALFORMATION; BILATERAL

HEAD

(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND  
MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION;  
MALPOSITIONED OR ABSENT MOUTH, MICROSTOMIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 426 (CONT.)

Fetal Position: Right 01 \*

Unique Fetal Id.: 5

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

ANUS

(External)

ANUS, ANAL ATRESIA - MALFORMATION

EYES

(External)

EYE(S), MACROPHthalmia - MALFORMATION; BILATERAL EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

TAIL

(External)

TAIL, SHORT - MALFORMATION

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MICROSTOMIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

(Visceral)

PALATE, CLEFT PALATE - MALFORMATION; SLIGHT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 426 (CONT.)

Unique Fetal Id.: 7

Fetal Position: Right 03

RIBS (Skeletal) RIB(S), FUSED - MALFORMATION; RIGHT 11 AND 12, MIDDLE

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; SEVERAL LUMBAR ARCHES--FUSED; LUMBAR CENTRA--HEMI-, BIPARTITE AND/OR FUSED

SKULL (Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; LEFT MACROPHTHALMIA: LEFT EYE SOCKET--LARGE TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

EYES (External) EYE(S), MACROPHTHALMIA - MALFORMATION; LEFT EYELID(S), OPEN EYELID(S) - MALFORMATION; LEFT

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, ABSENT; RIGHT, SMALL IN SIZE AND MALPOSITIONED DORSAL, HEMATOMA - VARIATION MOUTH, MICROSTOMIA - MALFORMATION

Unique Fetal Id.: 8

Fetal Position: Right 04 \*

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; MULTIPLE/SMALL IN SIZE FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 426 (CONT.)

Fetal Position: STERNUM (Skeletal)	Right 05	Unique Fetal Id.: 9
		STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT

VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; RIGHT LUMBAR ARCHES 3 AND 4--FUSED; LEFT SIDES OF LUMBAR CENTRA 4 AND 5--FUSED; LEFT LUMBAR ARCH 7--SMALL

SKULL  
(Skeletal)

TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

HEAD  
(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position: Right 06 \*

Unique Fetal Id.: 10

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

EYES  
(External)

EYE(S), MACROPHthalmia - MALFORMATION; LEFT EYELID(S), OPEN EYELID(S) - MALFORMATION; LEFT

ABDOMEN  
(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT

HEAD  
(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, ABSENT; RIGHT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MICROSTOMIA - MALFORMATION PALATE, CLEFT PALATE - MALFORMATION; SLIGHT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 426 (CONT.)

Fetal Position: Right 07  
STERNUM  
(Skeletal)

Unique Fetal Id.: 11

STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT

VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION CENTRA, BIPARTITE - VARIATION;  
LUMBAR 1-5

SKULL

(Skeletal)

TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD

(External)

PINNA (E), PINNA (E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND  
MALPOSITIONED FACIAL PAPILLA (E), FACIAL PAPILLA (E) ANOMALY - MALFORMATION;  
SUPERNUMERARY; MALPOSITIONED OR ABSENT MOUTH, MICROSTOMIA - MALFORMATION

Fetal Position: Right 08 \*

Unique Fetal Id.: 12

Comments: EXTERNALS CONFIRMED VISCERALLY

EYES

(External)

EYE(S), MACROPHTHALMIA - MALFORMATION; RIGHT EYELID(S), OPEN EYELID(S) -  
MALFORMATION; BILATERAL

HEAD

(External)

PINNA (E), PINNA (E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND  
MALPOSITIONED MOUTH, MICROSTOMIA - MALFORMATION  
PALATE, CLEFT PALATE - MALFORMATION; SLIGHT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 426 (CONTR.)

Fetal Position: Right 09 Unique Fetal Id.: 13

RIBS (Skeletal)

RIB 14, RUDIMENTARY - VARIATION; LEFT

STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT

VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MICROSTOMIA - MALFORMATION

Animal: 430

Unique Fetal Id.: 1

Fetal Position: Left 01

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

ABDOMEN

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION

(Visceral)

MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION; SLIGHT

(External)

JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

(Visceral)

PALATE, CLEFT PALATE - MALFORMATION; SLIGHT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 430 (CONT.)

Fetal Position: Left 02 Unique Fetal Id.: 2

RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; RIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

HEAD (External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

Fetal Position: Left 03 \* Unique Fetal Id.: 3

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION (Visceral) PALATE, CLEFT PALATE - MALFORMATION; SLIGHT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 430 (CONT.)

Fetal Position: Left 04 Unique Fetal Id.: 4

RIBS (Skeletal) RIB 14, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN (Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE/RIBS, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; RIGHT VERTEBRAL ARCHES 13 AND 14--FUSED; RIGHT RIBS 13 AND 14--FUSED EXCEPT AT ARTICULATING HEADS; THORACIC VERTEBRA 12--MALALIGNED; LUMBAR CENTRUM 1--FORMED ON LEFT SIDE ONLY

SKULL

(Skeletal) TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

HEAD

(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; RIGHT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

Fetal Position: Left 05 \* Unique Fetal Id.: 5

Comments: EXTERNALS CONFIRMED VISCERALLY

EYES

(External) EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL MICROPHTHALMIA

HEAD

(External) HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; RIGHT, SMALL IN SIZE BRAIN, EXENCEPHALY - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 430 (CONT.)

Fetal Position: Left 06 Unique Fetal Id.: 6

RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; RIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; ENCEPHALOCELE: LARGE GAP BETWEEN PARIETALS

HEAD (External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT BRAIN, ENCEPHALOCELE - MALFORMATION

Fetal Position: Left 07 \* Unique Fetal Id.: 7

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

ABDOMEN (Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT

HEAD (External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 430 (CONT.)

Fetal Position:	Right 01	Unique Fetal Id.: 8
STERNUM	(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

VERTEBRAL COLUMN	(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
------------------	------------	---

SKULL	(Skeletal)	SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: LARGE PORTIONS OF FRONTALS, PARIETALS, INTERPARIETAL--ABSENT, SUPRAOCCIPITAL--REDUCED OSSIFICATION; MAXILLAE MICROGNATHIA TYMPANIC RING(S), ABSENT - MALFORMATION; RIGHT
-------	------------	---

EYES	(External)	EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL
------	------------	---

HEAD	(External)	FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION
------	------------	--

Fetal Position:	Right 02 *	Unique Fetal Id.: 9
-----------------	------------	---------------------

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

ABDOMEN	(Visceral)	KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT
---------	------------	--

HEAD	(External)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; RIGHT, SMALL IN SIZE FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION
------	------------	---



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 430 (CONT.)

Fetal Position: Right 03 Unique Fetal Id.: 10

RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; RIGHT

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) HYOID, UNOSSIFIED - VARIATION TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

Fetal Position: Right 04 \* Unique Fetal Id.: 11

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT BRAIN, ENCEPHALOCELE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 430 (CONT.)

Fetal Position: Right 06 \*

Unique Fetal Id.: 13

Comments: LEFT MICROPTHALMIA NOT CONFIRMED SKELETALLY

### STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT

### VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; LUMBAR VERTEBRAE 4, 5 AND 6--MALALIGNED

### SKULL

(Skeletal)

SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPTHALMIA - MALFORMATION; LEFT MICROPTHALMIA

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

Animal: 432

Fetal Position: Left 01 \*

Unique Fetal Id.: 1

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 432 (CONT.)

Fetal Position: Left 02 \* Unique Fetal Id.: 2

Comments: RIGHT MICROPTHALMIA NOT CONFIRMED SKELETALLY

### RIBS

(Skeletal)

RIB 14, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY

### VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE/RIBS, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; RIGHT THORACIC ARCHES 12 AND 13--FUSED; RIGHT RIBS 12 AND 13--FUSED BETWEEN (BUT NOT INCLUDING) PROXIMAL ENDS AND MIDDLE

### SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: LARGE PORTIONS OF FRONTALS, PARIETALS, INTERPARIETAL--ABSENT; MAXILLAE MICROGNATHIA; MANDIBULAR MICROGNATHIA TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPTHALMIA - MALFORMATION; RIGHT MICROPTHALMIA EYELID(S), OPEN EYELID(S) - MALFORMATION; LEFT

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION MOUTH, CORNER, FLESHY PROTUBERANCE - MALFORMATION; RIGHT JAW, MAXILLAE, MICROGNATHIA - MALFORMATION JAW, MANDIBLE, MICROGNATHIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 432 (CONT.)

Fetal Position: Left 03 \* Unique Fetal Id.: 3

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED OR ABSENT

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

TAIL

(External)

TAIL, SHORT AND BENT - MALFORMATION

BACK

(External)

BACK, SPINA BIFIDA - MALFORMATION

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 432 (CONT.)

Fetal Position: Left 04 Unique Fetal Id.: 4

RIBS (Skeletal) RIB 14, FULL - VARIATION; BILATERAL

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: LARGE PORTIONS OF FRONTALS, PARIETALS, INTERPARIETAL--ABSENT; MANDIBULAR MICROGNATHIA; MAXILLAE MICROGNATHIA TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

EYES (External) EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION JAW, MANDIBLE, MICROGNATHIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 432 (CONT.)

Fetal Position: Left 05 \* Unique Fetal Id.: 5

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

ANUS

(External)

ANUS, ANAL ATRESIA - MALFORMATION

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

TAIL

(External)

TAIL, SHORT - MALFORMATION

BACK

(External)

BACK, SPINA BIFIDA - MALFORMATION

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MICROSTOMIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 432 (CONT.)

Fetal Position: Left 06 Unique Fetal Id.: 6

ANUS (External) ANUS, ANAL ATRESIA - MALFORMATION

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; 28 PRESACRAL VERTEBRAE; BILATERAL LUMBAR ARCHES 3, 4 AND 5--FUSED; CENTRA--FUSED, PARTLY ABSENT AND/OR MALFORMED; SACRAL VERTEBRAE MALFORMED VERTEBRAE, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; SHORT TAIL: NO CAUDAL VERTEBRAE

SKULL (Skeletal) SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

TAIL (External) TAIL, SHORT - MALFORMATION

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position: Right 01 \* Unique Fetal Id.: 7

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

HEAD (External) HEAD, CEPHALOCELE - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 432 (CONT.)

Fetal Position: Right 02

Unique Fetal Id.: 8

VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; LEFT THORACIC ARCH 13 AND LEFT LUMBAR ARCH 1--FUSED; LEFT LUMBAR ARCHES 3 AND 4--FUSED; THORACIC CENTRUM 11 THROUGH LUMBAR CENTRUM 4--BIPARTITE AND/OR MALALIGNED

SKULL

(Skeletal)

SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position: Right 03 \*

Unique Fetal Id.: 9

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

ANUS

(External)

ANUS, ANAL ATRESIA - MALFORMATION

TAIL

(External)

TAIL, SHORT AND BENT - MALFORMATION

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED/SMALL/SUPERNUMERARY FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MICROSTOMIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 432 (CONT.)

Fetal Position: Right 04 Unique Fetal Id.: 10

RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; RIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: FRONTALS AND PARIETALS BILATERAL--SMALL TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

HEAD (External) PINNA (E), PINNA (E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED/SMALL/SUPERNUMERARY FACIAL PAPILLA (E), FACIAL PAPILLA (E) ANOMALY - MALFORMATION; MALPOSITIONED BRAIN, EXENCEPHALY - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

Fetal Position: Right 05 \* Unique Fetal Id.: 11

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED OR ABSENT

EYES (External) EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

TAIL (External) TAIL, KINKY - MALFORMATION

HEAD (External) PINNA (E), PINNA (E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA (E), FACIAL PAPILLA (E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 432 (CONT.)

Fetal Position: Right 06  
ANUS

Unique Fetal Id.: 12

(External)

ANAL OPENING, SMALL IN SIZE - MALFORMATION

RIBS

(Skeletal)

RIB 14, RUDIMENTARY - VARIATION; LEFT

VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; 28 PRESACRAL VERTEBRAE;  
LUMBAR VERTEBRAE--MALFORMED AND/OR FUSED VERTEBRAE, CONFIRMATION OF EXTERNAL  
FINDI - CONFIRMATION; KINKY TAIL: CAUDAL VERTEBRAE--MALALIGNED

SKULL

(Skeletal)

TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

TAIL

(External)

TAIL, KINKY - MALFORMATION

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND  
MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION;  
SUPERNUMERARY MOUTH, MICROSTOMIA - MALFORMATION

Fetal Position: Right 07 \*

Unique Fetal Id.: 13

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND  
MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION;  
SUPERNUMERARY MOUTH, CORNER, FLESHY PROTUBERANCE - MALFORMATION; BILATERAL

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 442

Fetal Position: Left 01 \* Unique Fetal Id.: 1

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED

Fetal Position: Left 02

Unique Fetal Id.: 2

RIBS

(Skeletal)

RIB 14, RUDIMENTARY - VARIATION; BILATERAL

STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT

VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), ABSENT - MALFORMATION; RIGHT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; RIGHT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Left 04

Unique Fetal Id.: 4

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 442 (CONT.)

Fetal Position: Left 05  
STERNUM (Skeletal)

Unique Fetal Id.: 5

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT

SKULL (Skeletal)

SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; MULTIPLE FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position: Left 06 \*

Unique Fetal Id.: 6

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

Fetal Position: Left 07  
RIBS (Skeletal)

Unique Fetal Id.: 7

RIB 14, RUDIMENTARY - VARIATION; RIGHT

VERTEBRAL COLUMN (Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; LEFT LUMBAR ARCHES 1 AND 2--FUSED

SKULL

(Skeletal)

SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SEVERE

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 442 (CONT.)

Fetal Position: Right 01 \* Unique Fetal Id.: 8

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED

### HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED BRAIN, ENCEPHALOCELE - MALFORMATION

Fetal Position: Right 02

Unique Fetal Id.: 9

### RIBS

(Skeletal)

RIB 14, RUDIMENTARY - VARIATION; BILATERAL

### STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

### VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal)

SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SEVERE TYMPANIC RING(S), ABSENT - MALFORMATION; RIGHT

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; MULTIPLE FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 442 (CONT.)

Fetal Position: Right 03 \* Unique Fetal Id.: 10

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; RIGHT MICROPHTHALMIA

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; MULTIPLE; RIGHT, MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Right 04

Unique Fetal Id.: 11

RIBS (Skeletal)

RIB 14, RUDIMENTARY - VARIATION; LEFT

VERTEBRAL COLUMN (Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal)

SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; RIGHT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position: Right 06

Unique Fetal Id.: 13

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 442 (CONT.)

Fetal Position: Right 07  
VERTEBRAL COLUMN  
(Skeletal)

Unique Fetal Id.: 14

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SEVERE TYMPANIC RING(S), UNOSSIFIED - VARIATION; RIGHT

HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position: Right 08 \*

Unique Fetal Id.: 15

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED OR ABSENT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; RIGHT, SMALL IN SIZE FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT MOUTH, MACROSTOMIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 445

Fetal Position: Left 01 Unique Fetal Id.: 1

RIBS (skeletal) RIB 14, RUDIMENTARY - VARIATION; BILATERAL

STERNUM (skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT

VERTEBRAL COLUMN (skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (skeletal) SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SEVERE

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 4 PRESENT DORSAL, HEMATOMA - VARIATION

Fetal Position: Left 02 \* Unique Fetal Id.: 2

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

HEAD (External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 4 PRESENT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 445 (CONT.)

Fetal Position: Left 04 Unique Fetal Id.: 4

RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; BILATERAL

STERNUM (Skeletal) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; DOMED HEAD SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

HEAD (External) HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

Fetal Position: Right 01 \* Unique Fetal Id.: 6

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

EYES (External) EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT ANOPHTHALMIA

HEAD (External) HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 445 (CONT.)

Unique Fetal Id.: 7

Fetal Position: Right 02

RIBS (Skeletal) RIB 14, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SEVERE TYMPANIC RING(S), UNOSSIFIED - VARIATION; RIGHT

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

Unique Fetal Id.: 8

Fetal Position: Right 03 \*

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

HEAD (External) HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 445 (CONT.)

Fetal Position: Right 04 Unique Fetal Id.: 9  
RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; BILATERAL

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL

HEAD (External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 4 PRESENT

Fetal Position: Right 05 \* Unique Fetal Id.: 10

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position: Right 06 Unique Fetal Id.: 11  
RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; LEFT

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 445 (CONT.)

Fetal Position: Right 07 \*

Unique Fetal Id.: 12

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED OR ABSENT

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; MALPOSITIONED/SMALL/SUPERNUMERARY FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT MOUTH, MICROSTOMIA - MALFORMATION

Fetal Position: Right 08

Unique Fetal Id.: 13

### RIBS

(Skeletal)

RIB 14, FULL - VARIATION; BILATERAL

### STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT

### VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal)

SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL

### HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

Fetal Position: Right 09 \*

Unique Fetal Id.: 14

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 445 (CONT.)

Fetal Position:	Right 10	Unique Fetal Id.: 15
RIBS		
(Skeletal)	RIB 14, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
SKULL		
(Skeletal)	SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), UNOSSIFIED - VARIATION; RIGHT	
HEAD		
(External)	FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT	

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 465

Fetal Position: Left 01 Unique Fetal Id.: 1

RIBS

(Skeletal)

RIB 14, FULL - VARIATION; BILATERAL

STERNUM

(Skeletal)

STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: LARGE PORTIONS OF FRONTALS, PARIETALS, INTERPARIETALS ABSENT; ANOPHTHALMIA: LEFT EYE SOCKET MALFORMED; CLEFT PALATE; MAXILLAE MICROGNATHIA; MANDIBULAR MICROGNATHIA SUPRAOCCIPITAL, REDUCED OSSIFICATION - VARIATION SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT ANOPHTHALMIA EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION JAW, MANDIBLE, MICROGNATHIA - MALFORMATION

APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 465 (CONT.)

Fetal Position: Left 02 \* Unique Fetal Id.: 2

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION;  
BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E)  
ANOMALY - MALFORMATION; ABSENT, ONLY 2 PRESENT BRAIN, ENCEPHALOCELE -  
MALFORMATION MOUTH, MICROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA -  
MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 465 (CONT.)

Unique Fetal Id.: 3

Fetal Position: Left 03  
RIBS

(Skeletal) RIB 14, FULL - VARIATION; BILATERAL

STERNUM

(Skeletal)

STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; ENCEPHALOCELE: PARIETALS--SMALL; LEFT ANOPHTHALMIA: LEFT EYE SOCKET--SMALL AND MALFORMED; DOMED HEAD; MAXILLAE MICROGNATHIA TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT ANOPHTHALMIA EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT BRAIN, ENCEPHALOCELE - MALFORMATION MOUTH, MICROSTOMIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 465 (CONT.)

Fetal Position: Left 05 \*

Unique Fetal Id.: 5

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

### HEAD

(External)

HEAD, CEPHALOCELE - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

(Visceral)

PALATE, CLEFT PALATE - MALFORMATION; MODERATE

Fetal Position:

Right 01

Unique Fetal Id.: 6

RIBS

(Skeletal)

RIB 14, FULL - VARIATION; BILATERAL

### STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

### VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: LARGE PORTIONS OF FRONTALS AND PARIETALS, INTERPARIETAL, SUPRAOCCIPITAL--ABSENT; BILATERAL ANOPHTHALMIA: EYE SOCKETS--SMALL AND MALFORMED; MAXILLAE MICROGNATHIA JUGAL(S), MALFORMED - MALFORMATION; BILATERAL SQUAMOSAL(S), MALFORMED - MALFORMATION; BILATERAL TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHthalmia - MALFORMATION; BILATERAL ANOPHTHALMIA

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 465 (CONT.)

Fetal Position: Right 02 \* Unique Fetal Id.: 7

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED OR ABSENT

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT MICROPHTHALMIA  
EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

### HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION;  
BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E)  
ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT

Fetal Position: Right 03

Unique Fetal Id.: 8

### RIBS

(Skeletal)

RIB 14, RUDIMENTARY - VARIATION; RIGHT

### STERNUM

(Skeletal)

STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

### VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal)

SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S),  
UNOSSIFIED - VARIATION; BILATERAL

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND  
MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION;  
MALPOSITIONED OR ABSENT MOUTH, MICROSTOMIA - MALFORMATION

APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 465 (CONT.)

Fetal Position: Right 04 \*

Unique Fetal Id.: 9

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED OR ABSENT

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL MICROPHTHALMIA  
EYELID(S), OPEN EYELID(S) - MALFORMATION; LEFT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND  
MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION;  
MALPOSITIONED OR ABSENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MICROSTOMIA -  
MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE,  
MICROGNATHIA - MALFORMATION JAW, MANDIBLE, MICROGNATHIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 465 (CONT.)

Fetal Position:	Right 05	Unique Fetal Id.: 10
RIBS (Skeletal)	RIB(S), FUSED - MALFORMATION; 7 AND 8, AT ARTICULATING HEADS ONLY RIB 14, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY	
STERNUM (Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
VERTEBRAL COLUMN (Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; BILATERAL CERVICAL ARCH 1 FUSED TO EXOCCIPITALS	
SKULL (Skeletal)	SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; LEFT MICROPHTHALMIA: LEFT EYE SOCKET--SMALL; RIGHT ANOPHTHALMIA: RIGHT EYE SOCKET--VERY SMALL AND MALFORMED; DOMED HEAD SQUAMOSAL(S), MALFORMED - MALFORMATION; BILATERAL	
EYES (External)	EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT MICROPHTHALMIA; RIGHT ANOPHTHALMIA	
HEAD (External)	HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT	



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 468

Fetal Position: Left 01 \* Unique Fetal Id.: 1

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL MICROPHTHALMIA

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT BRAIN, ENCEPHALOCELE - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION

Animal: 468

Fetal Position: Left 03 Unique Fetal Id.: 3

Sternum

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; ENCEPHALOCELE: GAP BETWEEN PARIETALS SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, SMALL IN SIZE; BILATERAL, MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, ENCEPHALOCELE - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 468 (CONT.)

Fetal Position: Right 01 \*

Unique Fetal Id.: 4

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; RIGHT MICROPHTHALMIA

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT BRAIN, EXENCEPHALY - MALFORMATION

Fetal Position: Right 02  
RIBS (Skeletal)

Unique Fetal Id.: 5

RIB 14, RUDIMENTARY - VARIATION; BILATERAL

STERNUM

(Skeletal)

STERNEBRA(E), 1-4, UNOSSIFIED - VARIATION; 3 AND 4 ONLY STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

VERTEBRAL COLUMN (Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION CERVICAL ARCHES, REDUCED OSSIFICATION - VARIATION; BILATERAL 2-6

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; DOMED HEAD; LEFT MICROPHTHALMIA: LEFT EYE SOCKET--SMALL AND MALFORMED SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT MICROPHTHALMIA EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 468 (CONT.)

Fetal Position: Right 03 \* Unique Fetal Id.: 6

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

BACK

(External)

BACK, MENINGOCELE - MALFORMATION

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION

Fetal Position: Right 04  
RIBS

(Skeletal)

Unique Fetal Id.: 7

RIB 14, RUDIMENTARY - VARIATION; BILATERAL

STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; ENCEPHALOCELE: POSTERIOR GAP BETWEEN PARIETALS SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, ENCEPHALOCELE - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 468 (CONT.)

Fetal Position: Right 06 \*

Unique Fetal Id.: 9

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

### ABDOMEN

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT URETER(S), HYDROURETER - VARIATION; BILATERAL, SLIGHT

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, ENCEPHALOCELE - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

Fetal Position: Right 07

Unique Fetal Id.: 10

STERNUM (skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

VERTEBRAL COLUMN (skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; THORACIC CENTRA 12 AND 13--MALALIGNED

SKULL (skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; DOMED HEAD; BILATERAL MICROPHTHALMIA: EYE SOCKETS BILATERAL--SMALL SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

EYES (External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL MICROPHTHALMIA

HEAD (External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 468 (CONT.)

Fetal Position: Right 08 \* Unique Fetal Id.: 11

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

EYES

(External) EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

HEAD

(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION

Animal: 476

Fetal Position: Left 01 \* Unique Fetal Id.: 1

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED

EYES

(External) EYE(S), MACROPTHALMIA - MALFORMATION; BILATERAL EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

BACK

(External) BACK, MENINGOCELE - MALFORMATION

HEAD

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED MOUTH, PALATE, CLEFT PALATE - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 476 (CONT.)

Fetal Position: Left 02 Unique Fetal Id.: 2

RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; BILATERAL

STERNUM (Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: LARGE PORTIONS OF FRONTALS AND PARIETALS BILATERAL ABSENT; MAXILLAE MICROGNATHIA; LEFT MACROPHTHALMIA: LEFT EYE SOCKET--LARGE SUPRAOCCIPITAL, REDUCED OSSIFICATION - VARIATION; MODERATE INTERPARIETAL, REDUCED OSSIFICATION - VARIATION; SEVERE SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), ABSENT - MALFORMATION; LEFT TYMPANIC RING(S), SMALL IN SIZE - MALFORMATION; RIGHT

EYES (External) EYE(S), MACROPHTHALMIA - MALFORMATION; LEFT EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD (External) FACIAL PAPILLA (E), FACIAL PAPILLA (E) ANOMALY - MALFORMATION; ABSENT, ONLY 4 PRESENT BRAIN, EXENCEPHALY - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 476 (CONT.)

Fetal Position: Left 03 \* Unique Fetal Id.: 3

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

THORACIC CAVITY  
(Visceral)

HEART, RIGHT SIDED AORTIC ARCH - MALFORMATION

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL MICROPHTHALMIA

ABDOMEN

(Visceral)

KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, MODERATE

HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

Fetal Position: Left 04  
VERTEBRAL COLUMN  
(Skeletal)

Unique Fetal Id.: 4

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; ENCEPHALOCELE: GAP BETWEEN PARIETALS; CLEFT PALATE SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, MODERATE TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, SMALL/SUPERNUMERARY FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, ENCEPHALOCELE - MALFORMATION MOUTH, MICROSTOMIA - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 476 (CONT.)

Fetal Position: Right 01 \* Unique Fetal Id.: 5

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

### EYES

(External) EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

### HEAD

(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION PALATE, CLEFT PALATE - MALFORMATION; SLIGHT

(Visceral)

Fetal Position: Right 02  
VERTEBRAL COLUMN (Skeletal)

Unique Fetal Id.: 6

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; LEFT LUMBAR ARCH 1--LARGE; LUMBAR CENTRUM 1--MALALIGNED

### SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: LARGE PORTIONS OF FRONTALS, PARIETALS, INTERPARIETAL, SUPRAOCCIPITAL--ABSENT; BILATERAL MICROPHTHALMIA: EYE SOCKETS BILATERAL--LARGE; MAXILLAE MICROGNATHIA TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

### EYES

(External)

EYE(S), MACROPHTHALMIA - MALFORMATION; BILATERAL EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

### HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MICROSTOMIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 476 (CONT.)

Fetal Position: Right 04 \* Unique Fetal Id.: 8

Comments: EXTERNALS NOT CONFIRMED VISCERALLY

### HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position: Right 05

Unique Fetal Id.: 9

STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT

VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: LARGE PORTIONS OF PARIETALS, FRONTS, INTERPARIETAL, SUPRAOCCIPITAL--ABSENT; BILATERAL MACROPHTHALMIA: EYE SOCKETS--LARGE; MAXILLAE MICROGNATHIA SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SEVERE TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

### EYES

(External)

EYE(S), MACROPHTHALMIA - MALFORMATION; BILATERAL

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MICROSTOMIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 476 (CONT.)

Fetal Position: Right 06 \* Unique Fetal Id.: 10

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL MICROPHTHALMIA

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MICROSTOMIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

Fetal Position:  
VERTEBRAL COLUMN  
(Skeletal)

Right 07

Unique Fetal Id.: 11

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; LEFT SIDES OF LUMBAR CENTRA 3 AND 4--FUSED

SKULL

(Skeletal)

HYOID, UNOSSIFIED - VARIATION SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, MODERATE TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 4 PRESENT MOUTH, MICROSTOMIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 477

Unique Fetal Id.: 2

Left 02

Fetal Position:  
VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE/RIBS, MALFORMED, ABSENT, AND/OR FUSED - MALFORMATION; THORACIC ARCHES 12 AND 13--FUSED; RIGHT RIB 13 ABSENT; LEFT THORACIC ARCHES 11 AND 12--FUSED; FUSION, MALFORMATION OF SOME LUMBAR ARCHES AND CENTRA, INCLUDING CENTRA THAT ARE MALALIGNED, BIPARTITE AND/OR FORMED ONLY ON ONE SIDE

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; CLEFT PALATE SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SEVERE TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MACROSTOMIA - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION

Fetal Position: Left 03 \*

Unique Fetal Id.: 3

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, ENCEPHALOCELE - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 477 (CONT.)

Fetal Position: Left 04  
RIBS (Skeletal)

Unique Fetal Id.: 4

RIB(S), BENT, SLIGHT TO MODERATE - VARIATION; LEFT 12 RIB 14, RUDIMENTARY - VARIATION; RIGHT

VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: LARGE PORTIONS OF FRONTALS, PARIETALS, INTERPARIETAL, SUPRAOCCIPITAL--ABSENT; MAXILLAE MICROGNATHIA; MANDIBULAR MICROGNATHIA SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, ABSENT; RIGHT, SMALL IN SIZE AND MALPOSITIONED BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION JAW, MANDIBLE, MICROGNATHIA - MALFORMATION

Fetal Position: Left 05 \*

Unique Fetal Id.: 5

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, ABSENT FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, CORNER, FLESHY PROTUBERANCE - MALFORMATION; LEFT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 477 (CONT.)

Fetal Position: Left 06 Unique Fetal Id.: 6  
RIBS (Skeletal) RIB 14, RUDIMENTARY - VARIATION; BILATERAL

STERNUM (Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; BILATERAL MICROPHTHALMIA: LARGE EYE SOCKETS BILATERAL; CLEFT PALATE SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

EYES (External) EYE(S), MACROPHTHALMIA - MALFORMATION; BILATERAL EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD (External) PINNA (E), PINNA (E) ANOMALY - MALFORMATION; BILATERAL, ABSENT FACIAL PAPILLA (E), FACIAL PAPILLA (E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT MOUTH, PALATE, CLEFT PALATE - MALFORMATION

Fetal Position: Left 07 \* Unique Fetal Id.: 7

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE-SUPERNUMERARY

EYES (External) EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

HEAD (External) PINNA (E), PINNA (E) ANOMALY - MALFORMATION; LEFT, ABSENT; RIGHT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA (E), FACIAL PAPILLA (E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, MICROSTOMIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 477 (CONT.)

Unique Fetal Id.: 8

Fetal Position: Left 08

RIBS (Skeletal) RIB(S), FUSED - MALFORMATION; LEFT 11 AND 12--OUTER THIRD

STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT  
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE, MALFORMED, ABSENT AND/OR  
FUSED - MALFORMATION; LEFT LUMBAR ARCHES AND LEFT SIDES OF CENTRA 1 AND 2--FUSED;  
RIGHT LUMBAR ARCHES 2 AND 3--FUSED; LUMBAR CENTRUM 2--MALALIGNED

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; ENCEPHALOCELE: SMALL GAP  
BETWEEN FRONTALS, POSTERIORLY; CLEFT PALATE TYMPANIC RING(S), UNOSSIFIED -  
VARIATION; BILATERAL

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL  
PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN,  
ENCEPHALOCELE - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION

Fetal Position: Right 01 \*

Unique Fetal Id.: 9

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, ABSENT; RIGHT, SMALL IN SIZE AND  
MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION;  
ABSENT, ONLY 3 PRESENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA -  
MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, CORNER, FLESHY  
PROTUBERANCE - MALFORMATION; RIGHT

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 477 (CONT.)

Fetal Position: Right 02 Unique Fetal Id.: 10  
 VERTEBRAL COLUMN  
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL  
 (Skeletal) TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

HEAD  
 (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, ABSENT; RIGHT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY DORSAL, HEMATOMA - VARIATION MOUTH, CORNER, FLESHY PROTUBERANCE - MALFORMATION; RIGHT

Fetal Position: Right 03 \* Unique Fetal Id.: 11

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED OR ABSENT

HEAD  
 (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

Fetal Position: Right 04 Unique Fetal Id.: 12  
 RIBS  
 (Skeletal) RIB 13, REDUCED OSSIFICATION - VARIATION; LEFT 13, INTERRUPTED

VERTEBRAL COLUMN  
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL  
 (Skeletal) SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SLIGHT TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

HEAD  
 (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 477 (CONT.)

Fetal Position: Right 05 \* Unique Fetal Id.: 13

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, CORNER, FLESHY PROTUBERANCE - MALFORMATION; RIGHT

Fetal Position: Right 06

Unique Fetal Id.: 14

### RIBS

(Skeletal)

RIB 14, RUDIMENTARY - VARIATION; RIGHT

### STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

### VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal)

SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, ABSENT; RIGHT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 485

Unique Fetal Id.: 1

Fetal Position: Left 01

RIBS

(Skeletal)

RIB 14, RUDIMENTARY - VARIATION; LEFT

STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT  
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE, MALFORMED, ABSENT, AND/OR  
FUSED - MALFORMATION; BILATERAL CERVICAL ARCH 1 FUSED TO EXOCCIPITALS AND/OR  
MALFORMED

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; ENCEPHALOCELE: GAP BETWEEN  
PARIETALS; BILATERAL ANOPHTHALMIA: NO EYE SOCKETS BILATERAL; DOMED HEAD  
SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S),  
UNOSSIFIED - VARIATION; BILATERAL

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION;  
BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E)  
ANOMALY - MALFORMATION; ABSENT, ONLY 1 PRESENT BRAIN, ENCEPHALOCELE -  
MALFORMATION MOUTH, MICROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA -  
MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 485 (CONT.)

Fetal Position: Left 03 \* Unique Fetal Id.: 3  
Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

### EYES

(External) EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

### HEAD

(External) HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 2 PRESENT

Fetal Position: Left 04  
RIBS

Unique Fetal Id.: 4

RIB(S), FUSED - MALFORMATION; RIGHT 11 AND 12, AT POINT 1/3 OF THE WAY FROM PROXIMAL ENDS 7TH CERVICAL RIB, PRESENT - VARIATION; BILATERAL

### STERNUM

(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

### SKULL

(Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; DOMED HEAD; RIGHT MACROPHTHALMIA: EYE SOCKET RIGHT--LARGE; LEFT ANOPHTHALMIA: LEFT EYE SOCKET SEVERELY MALFORMED AND SMALL; MANDIBLE MALFORMED: MANDIBLE FORMED ON LEFT SIDE ONLY SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SEVERE TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

### EYES

(External) EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT ANOPHTHALMIA EYE(S), MACROPHTHALMIA - MALFORMATION; RIGHT EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

### HEAD

(External) HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, NONE PRESENT MOUTH, TONGUE, FORKED/FUSED TO MANDIBLE - MALFORMATION JAW, MANDIBLE, MALFORMED - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 485 (CONT.)

Fetal Position: Left 05 \* Unique Fetal Id.: 5

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED OR ABSENT

### EYES

(External)

EYE(S), MACROPHthalmia - MALFORMATION; RIGHT EYELID(S), OPEN EYELID(S) - MALFORMATION; RIGHT

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT MOUTH, MICROSTOMIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

Fetal Position: Left 06  
RIBS

Unique Fetal Id.: 6

(Skeletal)

RIB 14, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; DOMED HEAD; BILATERAL ANOPHTHALMIA: EYE SOCKETS BILATERAL--VERY SMALL SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), UNOSSIFIED - VARIATION; LEFT--REDUCED OSSIFICATION, RIGHT--UNOSSIFIED

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHthalmia - MALFORMATION; BILATERAL ANOPHTHALMIA

### HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT MOUTH, CORNER, FLESHY PROTUBERANCE - MALFORMATION; LEFT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 485 (CONT.)

Fetal Position: Right 01 \* Unique Fetal Id.: 7

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

### EYES

(External)

EYE(S), MACROPHthalmia - MALFORMATION; BILATERAL EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT MOUTH, MICROSTOMIA - MALFORMATION

Fetal Position: Right 03  
VERTEBRAL COLUMN (Skeletal)

Unique Fetal Id.: 9

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; DOMED HEAD; BILATERAL ANOPHTHALMIA: EYE SOCKETS BILATERAL--MALFORMED SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, MODERATE TO SEVERE TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHthalmia - MALFORMATION; BILATERAL ANOPHTHALMIA

### HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 1 PRESENT MOUTH, MICROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 485 (CONT.)

Fetal Position: Right 04 \* Unique Fetal Id.: 10

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

### EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

### HEAD

(External)

HEAD, CEPHALOCELE - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 2 PRESENT MOUTH, MICROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION MOUTH, CORNER, FLESHY PROTUBERANCE - MALFORMATION; LEFT

Fetal Position: Right 05

Unique Fetal Id.: 11

### RIBS

(Skeletal)

RIB 14, RUDIMENTARY - VARIATION; BILATERAL

### STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

### VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; ENCEPHALOCELE: LARGE GAP BETWEEN PARIETALS; DOMED HEAD; CLEFT PALATE SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; LEFT

### HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED BRAIN, ENCEPHALOCELE - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 485 (CONT.)

Fetal Position: Right 06 \*

Unique Fetal Id.: 12

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED OR ABSENT

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

Fetal Position:

Right 07

Unique Fetal Id.: 13

RIBS

(Skeletal)

RIB 14, RUDIMENTARY - VARIATION; BILATERAL

STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; DOMED HEAD; BILATERAL ANOPHTHALMIA: EYE SOCKETS BILATERAL--MALFORMED SQUAMOSAL(S), UNOSSIFIED - VARIATION; BILATERAL TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL ANOPHTHALMIA

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT MOUTH, MICROSTOMIA - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 493

Fetal Position: Left 03

Unique Fetal Id.: 3

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; CLEFT PALATE JUGAL(S), UNOSSIFIED - VARIATION; BILATERAL SQUAMOSAL(S), UNOSSIFIED - VARIATION; BILATERAL

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, ABSENT FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, PALATE, CLEFT PALATE - MALFORMATION

Fetal Position: Left 05 \*

Unique Fetal Id.: 5

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; LEFT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION; BILATERAL JAW, MAXILLAE, MICROGNATHIA - MALFORMATION JAW, MANDIBLE, MICROGNATHIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 493 (CONT.)

Fetal Position: Right 04 Unique Fetal Id.: 9  
 STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: LARGE PORTIONS OF FRONTALS, PARIETALS, INTERPARIETAL ABSENT; MAXILLAE MICROGNATHIA TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

EYES (External) EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL MICROPHTHALMIA

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

Fetal Position: Right 06 \* Unique Fetal Id.: 11

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

EYES (External) EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; RIGHT ANOPHTHALMIA

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED OR ABSENT PALATE, CLEFT PALATE - MALFORMATION; SLIGHT



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 496

Fetal Position: Left 01 \* Unique Fetal Id.: 1

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; BILATERAL MICROPHTHALMIA

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; RIGHT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position:  
VERTEBRAL COLUMN  
(Skeletal)

Left 02

Unique Fetal Id.: 2

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

SQUAMOSAL(S), UNOSSIFIED - VARIATION; BILATERAL

HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED

Fetal Position: Left 03 \*

Unique Fetal Id.: 3

Comments: EXTERNALS NOT CONFIRMED VISCERALLY

HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 496 (CONT.)

Fetal Position: Left 04 \* Unique Fetal Id.: 4

Comments: RIGHT MICROPTHALMIA NOT CONFIRMED SKELETALLY

### STERNUM

(Skeletal) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 5, SLIGHT

### VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal) SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SLIGHT

### EYES

(External) EYE(S), ANOPHTHALMIA/MICROPTHALMIA - MALFORMATION; RIGHT MICROPTHALMIA

### HEAD

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY/MALPOSITIONED

Fetal Position: Left 05 \* Unique Fetal Id.: 5

Comments: EXTERNALS NOT CONFIRMED VISCERALLY

### HEAD

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

### Fetal Position:

Left 06 Unique Fetal Id.: 6

### VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal) SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; RIGHT, SLIGHT TYMPANIC RING(S), UNOSSIFIED - VARIATION; RIGHT

### HEAD

(External) FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 496 (CONT.)

Fetal Position: Left 07 \* Unique Fetal Id.: 7

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, SMALL IN SIZE FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY

Fetal Position: Left 08

Unique Fetal Id.: 8

VERTEBRAL COLUMN (Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal)

SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SLIGHT TYMPANIC RING(S), ABSENT - MALFORMATION; BILATERAL

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT

Fetal Position: Left 09 \*

Unique Fetal Id.: 9

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--ABSENT

### HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; RIGHT, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 4 PRESENT JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 496 (CONT.)

Fetal Position: Right 01 \* Unique Fetal Id.: 10

Comments: RIGHT

RIBS

(Skeletal)

RIB 14, RUDIMENTARY - VARIATION; LEFT

VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: LARGE PORTIONS OF FRONTALS, PARIETALS, INTERPARIETAL, SUPRAOCCIPITAL--ABSENT; MAXILLAE MICROGNATHIA; BILATERAL MICROPTHALMIA: EYE SOCKETS BILATERAL--SMALL AND/OR MALFORMED SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL TYMPANIC RING(S), UNOSSIFIED - VARIATION

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPTHALMIA - MALFORMATION; BILATERAL MICROPTHALMIA

HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

Fetal Position: Right 02 \*

Unique Fetal Id.: 11

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPTHALMIA - MALFORMATION; RIGHT ANOPHTHALMIA

HEAD

(External)

FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; MALPOSITIONED



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 496 (CONT.)

Fetal Position:	Right 03	Unique Fetal Id.: 12
STERNUM	(Skeletal)	STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT

SKULL	(Skeletal)	SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; DOMED HEAD; EXENCEPHALY; FRONTALS AND PARIETALS BILATERAL--SMALL; MAXILLAE MICROGNATHIA; BILATERAL MICROPTHALMIA: EYE SOCKETS BILATERAL--SMALL SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, MODERATE TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL
-------	------------	--

EYES	(External)	EYE (S), ANOPHTHALMIA/MICROPTHALMIA - MALFORMATION; BILATERAL MICROPTHALMIA
------	------------	---

HEAD	(External)	HEAD, DOMED HEAD - MALFORMATION PINNA (E), PINNA (E) ANOMALY - MALFORMATION; RIGHT, MALPOSITIONED FACIAL PAPILLA (E), FACIAL PAPILLA (E) ANOMALY - MALFORMATION; ABSENT, 3 OR 4 PRESENT BRAIN, EXENCEPHALY - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION
------	------------	--

Fetal Position:	Right 04 *	Unique Fetal Id.: 13
-----------------	------------	----------------------

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--MALPOSITIONED

EYES	(External)	EYE (S), ANOPHTHALMIA/MICROPTHALMIA - MALFORMATION; RIGHT MICROPTHALMIA
------	------------	---

HEAD	(External)	FACIAL PAPILLA (E), FACIAL PAPILLA (E) ANOMALY - MALFORMATION; MALPOSITIONED
------	------------	--

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 499

Unique Fetal Id.: 2

Fetal Position: Left 02  
RIBS

(Skeletal) RIB 14, FULL - VARIATION; BILATERAL

STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4  
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

VERTEBRAL COLUMN  
(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: LARGE  
PORTIONS OF FRONTALS, PARIETALS, INTERPARIETAL, SUPRAOCCIPITAL--ABSENT; LEFT  
ANOPHTHALMIA: LEFT EYE SOCKET--MALFORMED; MAXILLAE MICROGNATHIA; MANDIBULAR  
MICROGNATHIA; CLEFT PALATE TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

EYES

(External)

EYE(S), ANOPHTHALMIA/MICROPHTHALMIA - MALFORMATION; LEFT ANOPHTHALMIA EYELID(S),  
OPEN EYELID(S) - MALFORMATION; RIGHT

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND  
MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION;  
SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, PALATE, CLEFT PALATE -  
MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION JAW, MANDIBLE,  
MICROGNATHIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 499 (CONT.)

Fetal Position: Left 03 \* Unique Fetal Id.: 3  
 Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

### EYES

(External) EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

### HEAD

(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION JAW, MANDIBLE, MICROGNATHIA - MALFORMATION

Fetal Position: Left 04  
 RIBS (Skeletal)

Unique Fetal Id.: 4  
 RIB 14, RUDIMENTARY - VARIATION; BILATERAL

### STERNUM

(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 AND 3, SLIGHT

VERTEBRAL COLUMN (Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

### SKULL

(Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; CLEFT PALATE SQUAMOSAL(S), REDUCED OSSIFICATION - VARIATION; BILATERAL, SEVERE TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

### HEAD

(External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 499 (CONT.)

Fetal Position: Left 06 \*

Unique Fetal Id.: 6

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

EYES

(External)

EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL  
PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN,  
EXENCEPHALY - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW,  
MAXILLAE, MICROGNATHIA - MALFORMATION JAW, MANDIBLE, MICROGNATHIA - MALFORMATION



# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

## INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 499 (CONT.)

Unique Fetal Id.: 9

Fetal Position: Right 03

PELVIS

(Skeletal)

PUBIS, UNOSSIFIED - VARIATION; LEFT

RIBS

(Skeletal)

RIB 14, RUDIMENTARY - VARIATION; LEFT

STERNUM

(Skeletal)

STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; BILATERAL MACROPHTHALMIA: EYE SOCKETS BILATERAL--LARGE; DOMED HEAD; CLEFT PALATE SQUAMOSAL(S), UNOSSIFIED - VARIATION; BILATERAL TYMPANIC RING(S), UNOSSIFIED - VARIATION; BILATERAL

EYES

(External)

EYE(S), MACROPHTHALMIA - MALFORMATION; BILATERAL EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD

(External)

HEAD, DOMED HEAD - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; ABSENT, ONLY 3 PRESENT MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

Fetal Position: Right 05 \*

Unique Fetal Id.: 11

Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, ENCEPHALOCELE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION

# APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS  
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

Animal: 499 (CONT.)

Fetal Position: Right 06 Unique Fetal Id.: 12  
RIBS (Skeletal) RIB 14, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY

STERNUM (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skeletal) SKULL, CONFIRMATION OF EXTERNAL FINDI - CONFIRMATION; EXENCEPHALY: LARGE PORTIONS OF FRONTALS, PARIETALS, INTERPARIETAL, SUPRAOCCIPITAL--ABSENT; MAXILLAE MICROGNATHIA TYMPANIC RING(S), UNOSSIFIED - VARIATION; LEFT

EYES (External) EYELID(S), OPEN EYELID(S) - MALFORMATION; LEFT

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

Fetal Position: Right 07 \* Unique Fetal Id.: 13  
Comments: EXTERNALS CONFIRMED VISCERALLY EXCEPT FACIAL PAPILLAE--SUPERNUMERARY

EYES (External) EYELID(S), OPEN EYELID(S) - MALFORMATION; BILATERAL

HEAD (External) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, ABSENT FACIAL PAPILLA(E), FACIAL PAPILLA(E) ANOMALY - MALFORMATION; SUPERNUMERARY BRAIN, EXENCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION MOUTH, TONGUE, MACROGLOSSIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION JAW, MANDIBLE, MICROGNATHIA - MALFORMATION

APPENDIX D

UIC/TRL STUDY NO.: 154 DEVELOPMENTAL TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 1000 MG/KG/DAY (RETINOL PALMITATE)

NOTE: THE FETUSES FROM LITTERS 385, 392, 410, AND 417 SCHEDULED FOR SKELETAL EXAMINATION DISARTICULATED DURING PROCESSING. INDIVIDUAL FETAL SKELETAL EXAMINATIONS WERE NOT POSSIBLE.

DRAFT

APPENDIX 6

Protocol and Amendments



DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

DEVELOPMENTAL TOXICITY (SEGMENT II)  
STUDY OF WR238605 SUCCINATE IN RATS

1.0 PURPOSE OF THE STUDY:

The purpose of this study is to evaluate the embryo/fetal toxicity and the teratogenic potential of WR238605 Succinate in rats. The protocol conforms to the standards of the U.S. Food and Drug Administration (1966): Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use. The protocol for this study was approved by the UIC Animal Care Committee (Appendix 1).

2.0 SPONSOR:

2.1 Name: U.S. Army Medical Materiel  
Development Activity

2.2 Address: Fort Detrick  
Frederick, MD 21702-5009

2.3 Representative: George J. Schieferstein, Ph.D.

3.0 TESTING FACILITY:

3.1 Name: Toxicology Research Laboratory (TRL)

3.2 Address: University of Illinois at Chicago (UIC)  
Department of Pharmacology  
1940 W. Taylor St.  
Chicago, Illinois 60612-7353

3.3 Study Director: Barry S. Levine, D.Sc., D.A.B.T.

4.0 DATES:

4.1 Proposed Initiation of In-Life Phase: 10/12/94

4.2 Proposed Completion of In-Life Phase: 11/04/94

4.3 Proposed Study Completion Date 02/04/95  
(Draft Final Report):

DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

5.0 TEST ARTICLE

- 5.1 Name or Code No: WR238605 Succinate (base mole fraction = 0.8)  
8-[4-Amino-1-methylbutyl]amino]-2,6-dimethoxy-4-  
methyl-5-(3-trifluoromethyl-phenoxy)quinoline succinate  
CAS #106635-81-8  
Bottle number BM12562
- 5.2 TRL Chemical No: 0720614
- 5.3 Physical Description: Pale yellow powder
- 5.4 Storage Conditions to Maintain Stability:
- 5.4.1 Temperature: 0 to 4°C.
- 5.4.2 Humidity: Ambient conditions.
- 5.4.3 Light: Protect from light; amber bottle or silver foil covering.
- 5.4.4 Special Requirements: None.
- 5.5 Special Handling Procedures: Standard safety precautions will be followed including gloves, eye protection, mask, and lab coats.
- 5.6 Log of Test Article: The amount, date, identity of person(s) removing aliquots and the purpose for which each aliquot of the test article was removed from the batch will be documented. At termination of the study, unused test article may be returned to the Sponsor.

6.0 PERSONNEL:

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Reproductive Toxicologist	Ashraf F. Youssef, M.D., Ph.D.
Reproductive Scientist	Roberto A. Matamoros, D.V.M., Ph.D.
Teratologist (PAI)	Michael D. Mercieca, B.S.
Analytical Chemist	Adam Negrusz, Ph.D.
Clinical Veterinarian	James Artwohl, D.V.M., M.S., D.A.C.L.A.M.
Veterinarian Support	Documented in raw data
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Documented in raw data
Chemistry Specialist	Thomas Tolhurst, B.S.
Quality Assurance	Ronald C. Schoenbeck

DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

7.0 TEST SYSTEM:

- 7.1 Species: Rat
- 7.2 Strain: CD® (Virus Antibody Free)
- 7.3 Sex(s)/Number: 125 time-mated females (day 0 = day of vaginal plug detection) in two shipments (a few days apart)
- 7.4 Age of Animals: ~60 - 70 days old at study initiation.
- 7.5 Body Weight: ~200 - 250 g at study initiation.
- 7.6 Source of Animals: Charles River Breeding Laboratories, Inc. The specific source will be documented in the raw data.
- 7.7 Justification for Selection of Test System: The FDA requires the use of two animal species for preclinical developmental toxicity studies, typically the rat and rabbit. The CD® rat was selected for evaluation because; (1) it is one mammalian species accepted for use in embryo/fetal toxicity - teratogenicity studies; (2) this strain of rat has been demonstrated to be sensitive to developmental toxicants; (3) it has been used for nonclinical studies of developmental toxicity; (4) historical data and experience exist; and (5) it was specified by the Sponsor.
- 7.8 Procedure for Unique Identification of Test System: Each animal will be given a study-unique animal number (ear tag) by the Supplier. This number will also appear on a cage card visible on the front of each cage. The cage card will additionally contain the study number, test article identification, treatment group number and dose level. Cage cards will be color-coded as a function of treatment group. Raw data records and specimens will also be identified by the unique test animal number.
- 7.9 Housing: The animals will be housed in an AAALAC-accredited facility. Animals will be singly housed in polycarbonate cages with Anderson-bed-a-cob bedding (Heinold, Kankakee, Illinois) in a temperature (65-78°F) and humidity (30-70%) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 840 cm<sup>2</sup> area and 20 cm height, is adequate to house rats at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All animals will be routinely transferred to clean cages with fresh bedding once weekly.
- 7.10 Quarantine Procedure: Animals will be quarantined for at least 3 days, from receipt until dosing is initiated on day 6 of gestation. During the quarantine period, the animals will be observed daily for signs of illness, and all unusual observations will be reported to the Study Director, Toxicologist or Clinical Veterinarian. Animals will be examined during quarantine and approved for use by the Clinical Veterinarian prior to being placed on test.



# DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

Any sickly animals will be eliminated prior to the test animal selection process. If a selected animal appears sickly prior to initiation of treatment, it will be replaced by a healthy animal prior to initiation of treatment under the direction of the Study Director or Toxicologist. Quarantine release will be documented on the Clinical Veterinarian Log by the veterinarian prior to study initiation.

- 7.11 Food: Purina Certified Rodent Chow No. 5002 (PMI Feeds, Inc., St. Louis, MO) will be provided *ad libitum* from arrival until termination.
- 7.12 Water: Tap water from an automatic watering system in which the room distribution lines are flushed daily will be provided *ad libitum* from arrival until termination. The water is untreated with additional chlorine or HCl.
- 7.13 There are no known contaminants in the feed or water which are expected to influence the study. A copy of the feed certification will be kept with the study records. The results of bimonthly comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.
- 7.14 It is not known if the animals will experience pain or distress during the study. Analgesic or anesthetic agents will confound the ability to determine the toxic potential of the test article, and therefore will not be used. If an animal is in severe pain or distress, following consultation with the veterinary staff, it will be euthanized in accordance with standard operating procedures.

## 8.0 EXPERIMENTAL DESIGN:

### 8.1 Treatment Groups:

<u>Group No.</u>	<u>Treatment</u>	<u>Dose Level</u> <u>(mg base/kg/day)</u>	<u>Number of</u> <u>Females*</u>
1	Vehicle	0	25
2	WR238605 Succinate	3	25
3	WR238605 Succinate	10	25
4	WR238605 Succinate	30	25
5**	Vitamin A (Retinol Palmitate)	250,000 IU/kg/day (1g/kg/day)	25

\* Presumed pregnant

\*\* The positive control agent, will be administered orally at the specified dose on days 9 and 10 of gestation at a dosing volume of 5 ml/kg.



DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

Test article dose levels will be selected on the basis of a range-finding developmental toxicity study in rats (UIC/TRL Study No. 153). The number of animals, 25/dose level, is the number of animals required by the *1966 FDA Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use* (Goldenthal Guidelines), and is the number of animals indicated by the Sponsor in Task Order UIC-10.

- 8.2 Frequency and Route of Administration of Test Article: The test article will be administered once daily by gavage during the period of major organogenesis, gestation days 6 through 15. It will be given at a dosing volume of 5 ml/kg. The control group will receive the vehicle at the same dosing volume. The specific volume to be administered will be adjusted on the basis of the animal's most recent body weight.
- 8.3 Justification of Route(s): The oral route is a convenient and accepted procedure for administering a specific amount of a test article to each animal. It mimics potential human exposure conditions and is specified by the Sponsor.
- 8.4 Procedure to Control Bias during the Assignment of Animals to Treatment Groups: During the quarantine/pretest period, animals judged to be healthy and meeting acceptable body weight requirements will be assigned to the study at random using a randomization procedure on the basis of body weight.
- 8.5 Test Article Vehicle: 1% Methylcellulose/0.2% Tween 80.
- 8.6 Test Article Dosage Form Preparation and Analyses: The dosage formulations of the test article will be prepared once at the beginning of the study. Stability data obtained from a previous study (UIC/TRL Study No. 047) indicated that dosing suspensions are stable for two weeks. Homogeneity data obtained from UIC/TRL Study No. 047 demonstrated that the test article suspensions are homogeneous (coefficients of variation for sampling in the top, middle and bottom of several test suspensions were typically less than 4%).

The stock test article suspension will be prepared by suspending the appropriate quantity of test article in the vehicle. All dosing suspensions will be stored at 0 - 4°C. Samples of the dosage formulations will be analyzed for test article concentration prior to use. Only samples within 10% of their intended concentration will be used. The dosing suspensions will be re-analyzed at the end of the dosing period.

- 8.7 Frequency of Observations, Test Analyses and Measurements:
- 8.7.1 Mortality Check: All animals will be observed twice daily, at least six hours apart for moribundity/mortality.
- 8.7.2 Clinical Signs: All animals will be observed daily for clinical signs of toxicity approximately 1-2 hours after dosing (days 6-15), and in the morning after completion of the dosing period (days 16-20). Moribund animals will be sacrificed on that day and the uterine contents will be examined as described in Section 3.7.6.

# DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

- 8.7.3 Body Weights: Individual body weights will be recorded on day 0 of gestation (the day a vaginal plug is observed), on the day of randomization, and on gestation days 6 - 15, 18 and 20.
- 8.7.4 Food Consumption: Food consumption for all animals will be measured during the following intervals: days 6 - 10; 10 - 15; 15 - 20.
- 8.7.5 Sacrifice: On day 20 of presumed gestation, all surviving female rats will be euthanized by carbon dioxide asphyxiation followed immediately by cesarean section.
- 8.7.6 Cesarean-Sectioning Observations: The abdominal and thoracic cavities will be opened by a ventral midline incision and the contents examined. In gravid animals, the ovaries will be examined. The number of corpora lutea on each ovary will be recorded (ovaries discarded after evaluation). The gravid uterus will be examined and weighed. The number and location of viable and nonviable fetuses\* *in utero*, early and late resorptions\*\* and the total number of implantation sites will be recorded.

The uterine position of each fetus will be documented using the following procedure. All implantation sites, including resorptions, will be numbered in consecutive fashion beginning with the left distal uterine horn, noting the position of the cervix. Maternal tissues will only be saved for histopathological examination in 10% neutral buffered formalin as deemed necessary by the gross findings. The carcass of each dam will then be discarded.

\*A viable fetus is defined as one which responds to stimuli. A non viable fetus is defined as a term fetus, which does not respond to stimuli *in utero* or is not breathing.

\*\*An early resorption is defined as one in which it is not grossly evident that organogenesis has occurred. A late resorption is defined as one in which it is grossly evident that organogenesis has occurred. A fetus with evident autolysis is considered a late resorption.

- 8.7.7 Confirmation of Pregnancy: Uteri from females that appear nongravid will be opened and placed for approximately 10 minutes in ammonium sulfide solution (0.5%) for detection of possible implantation sites. If implantation sites are detected, the ovaries will be examined as in 8.7.6.
- 8.7.8 Necropsy: Animals which die on test or are sacrificed if moribund will be examined as soon as possible for the cause of death. Examination will not be performed if precluded by postmortem autolysis. Pregnancy status and uterine contents will be recorded. Maternal tissues with gross lesions appropriate for retention will be fixed in neutral buffered 10% formalin for possible future



evaluation. Viscera which appear normal will be discarded. Naturally-delivered pups will be examined to the extent possible using the same methods described for fetuses.

8.7.9 Fetal Gross Observations: The number of fetuses will be recorded. Each fetus will be sexed and weighed, and will be individually identified noting litter, uterine placement and study number. All of the fetuses will be euthanized by an ip injection of a 40% solution of sodium pentobarbital (0.04 ml/fetus). Subsequently, a morphological examination will be performed as noted in Section 8.7.10.

8.7.10 Fetal Morphological Examination:

8.7.10.1 External: A detailed examination of each fetus will be conducted to include the eyes, palate, head shape and extremities. Any abnormal finding will be recorded.

8.7.10.2 Visceral Evaluation: One-half of the viable and nonviable fetuses from each litter will be fixed in Bouin's solution for subsequent examination. Following fixation, each fetus will be examined using the Wilson free-hand slicing technique (Wilson, 1965).

8.7.10.3 Skeletal Evaluation: The remaining viable and nonviable fetuses in each litter will be eviscerated and the skeletons will be examined for alterations following staining with Alizarin Red S and then cleared in glycerin as recommended by Dawson (Dawson, 1926). Skeletal preparations will be stored in glycerin 100% and will be retained.

8.7.11 Statistical Analyses: Maternal body weights and weight gains, uterine absolute and relative weight (% body weight), maternal food consumption and mean fetal body weights will be analyzed by a one-way analysis of variance. If a significant F ratio is obtained ( $p \leq 0.05$ ), Dunnett's test will be used for pair-wise comparisons to the control group.

The incidence of fetal abnormalities will be examined in terms of the fetal and litter percentages (% abnormal fetuses/group & % abnormal litters/group). Abnormalities will include malformations in addition to variations. The proportions of litters with abnormalities and male to female fetal sex ratios will be compared by using the Chi-square test criterion with Yate's correction for 2 x 2 contingency tables and/or Fisher's exact probability test.

DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

The mean numbers of resorptions, nonviable fetuses, viable fetuses, corpora lutea (C.L.), implantations, preimplantation loss\* and postimplantation deaths\*\* will be compared using the Kruskal-Wallis test. If a significant effect is seen ( $p \leq 0.05$ ), the Mann-Whitney U test will be used for pairwise comparisons to the control group.

\*Preimplantation loss = # C.L. - # implantations

\*\*Postimplantation death = # implantations - # live fetuses

Other statistical analyses will be conducted as deemed necessary and will be documented in the raw data.

In addition to the written report, summary data tables of parameters and variability will be transmitted to the Sponsor on magnetic media (computer diskette) in "ASCII" form. The transcribed data on disk will no longer be considered GLP compliant.

#### 9.0 RECORDS TO BE MAINTAINED:

All data generated during the conduct of the study, except those that are generated as direct computer input, shall be recorded directly, promptly, and accurately in ink in bound books with prenumbered pages or on worksheets that shall be bound during or at the conclusion of the nonclinical laboratory study. All appropriate computer and machine output shall be bound during or at the conclusion of the study. All data entries shall be dated on the day of entry and signed or initialed by the person entering the data.

Any changes in entries for whatever reason (e.g., to correct an error or transposition) shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of data input. In computer driven collection systems, the operator responsible for direct data input shall be identified at the time of data input. Any changes in computer entries for whatever reason (e.g., to correct an error or transposition) shall be made in such a manner so as not to obscure the original entry, if possible, shall indicate the reason for such change, and shall be dated and signed by the responsible individual.

All recorded data shall be reviewed, signed, and dated by a knowledgeable person, other than the person making the entry, to assure adherence to procedures and to verify observations.

Upon completion of the study and submission of the final report, all raw data, documentation, specimens, test article reserves and other materials necessary to reconstruct the study will be stored in the TRL archives maintained by Quality Assurance.

All changes or revisions, and reasons therefore, to this protocol once it is approved shall be documented, signed by the Study Director and Sponsor, dated and maintained with the protocol.



DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

10.0 REGULATORY REQUIREMENTS:

This study will be performed in compliance with the UIC/TRL Quality Assurance Program designed to conform with FDA Good Laboratory Practice Regulations and EPA Good Laboratory Practice Standards.

Will this study be submitted to a regulatory agency? Yes If so, to which agency(ies)? Food and Drug Administration

Does the Sponsor Request that remaining test article be returned? Possibly; direction will be provided by the Sponsor.

Does the Sponsor request that samples of the test article/carrier mixture(s) be returned to the Sponsor? No

11.0 REFERENCES:

Dawson, AB (1926). A note on the staining of cleared specimens with Alizarin Red S. Stain Technol. 1:123-124.

Dunnnett, CW (1955). A multiple comparison procedure for comparing several treatments with a control. J. Amer. Stat. Assoc. 50:1096-1129.

DTSC (1992). The assessment of developmental and reproductive risks. Toxicology and Risk Assessment Section, Department of Toxic Substances Control (DTSC), California Environmental Protection Agency, Sacramento, CA. Review Draft dated March, 1992.

EPA (1984b). Guideline for the health assessment of suspect developmental toxicants. Draft document from the Office of Research and Development, EPA, Washington, D.C.

EPA (1985). Hazard evaluation division standard evaluation procedure Teratology Studies. U.S. Environmental Protection Agency, Office of Pesticide Programs, document EPA-540/9.85.018.

FDA (1982). Toxicological principles for safety assessment of direct food additives and color additives used in food. Bureau of Foods, Food and Drug Administration, Washington, D.C.

Gad, S and Weil, CS (1988). Statistics and Experimental Design for Toxicologists, 2nd ed. pp 53-70, 147-176, Telforel Press. Caldwell, NJ.

Hayes, W (1989). Principles and Methods of Toxicology, pp 311-361, Raven press. New York, NY.

Lang, LP (1993). Historical control data for development and reproductive toxicity studies using the Crl:CD BR rat, p3, Charles River Laboratories.

DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

Snedecor, GW and Cochran, WG (1967). Variance test for homogeneity of the binomial distribution. Statistical Methods, 6th Edition, pp. 240-241, Iowa State University Press. Ames, IA.

U.S. Department of Health and Human Services (1985). Guide for the Care and Use of Laboratory Animals. Prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources. Commission on Life Sciences, National Research Council. Public Health Service, National Institutes of Health, NIH Publications No. 86-23.

U.S. Environmental Protection Agency (1991). Guidelines for developmental toxicity risk assessment. Notice. Fed. Regist. 56: 63798-63826.

U.S. Food and Drug Administration (1966). Guidelines for reproduction studies for safety evaluation of drugs for human use.

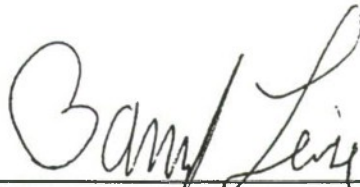
Wilson, JG (1965). Methods for administering drugs and detecting malformations in experimental animals. In: Teratology Principles and Techniques (Wilson, JG and Warkany, J. eds.). pp. 262-277, Un. Chicago Press. Chicago, IL.

DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

12.0 PROTOCOL APPROVAL:

STUDY DIRECTOR:

  
Barry S. Levine, D.Sc., D.A.B.T.

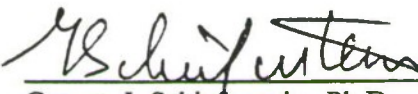
6/28/94  
Date

QUALITY ASSURANCE:

  
Ronald Schoenbeck

6/28/94  
Date

SPONSOR APPROVAL:

  
George J. Schieferstein, Ph.D.  
Contracting Officer's  
Representative (COR)

7/5/94  
Date

COMMENTS FROM THE COR:

Office of the Vice Chancellor for Research (M/C 672)  
310 Administrative Office Building  
1737 West Polk Street  
Chicago, Illinois 60612-7227  
(312) 996-4995

Appendix 1

June 22, 1994

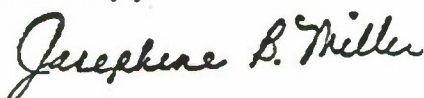
Barry S. Levine  
Pharmacology  
312 BGRC, M/C 868

Dear Dr. Levine:

The modifications requested in your correspondence of June 15, 1994 pertaining to your approved protocol ACC: #93-077-12: "Developmental Toxicity (Segment II) Study of WR238605 in Rats" have been reviewed in accordance with the Animal Care and Use Policies of the University of Illinois at Chicago. You will be pleased to know that the modifications were approved on June 20, 1994 and consequently the records of Animal Care Committee will be revised to reflect these changes.

Thank you for complying with the Animal Care Policies and Procedures of UIC.

Sincerely yours,



Josephine B. Miller, Ph.D.  
Chair, Animal Care Committee

JBM:st  
xc: BRL



# DRAFT

## PROTOCOL AMENDMENT

Study No.: 154  
Title: Developmental Toxicity (Segment II) Study of WR238605 Succinate in Rats

1. Page 1 Section 4

The following dates were assigned to the study

- |     |  |          |
|-----|--|----------|
| 4.1 | <u>Proposed Initiation of In-Life Phase (Day 0):</u>                   | 10/12/94 |
| 4.2 | <u>Proposed Completion of In-Life Phase:</u>                           | 11/04/94 |
| 4.3 | <u>Proposed Study Completion Date:</u><br><u>(Draft Final Report):</u> | 02/04/95 |

Reason: Dates were not decided at the time the protocol was submitted.

2. Page 3 Section 7.3

Add the following phrase "in two shipments (a few days apart)"

Reason: To clarify the procedure for receiving animal shipments.

3. Pages 4 and 5 Section 8.1

The following doses were assigned for Groups 1-5,

<u>Group No.</u>	<u>Treatment</u>	<u>Dose Level</u> <u>(mg base/kg/day)</u>
1	Vehicle	0
2	WR238605	3
3	WR238605	10
4	WR238605	30
5	(Retinol Palmitate)	250,000 IU/kg/day (1g/kg/day)

Reason: To reflect that the dose range-finding study has been done, from which dose levels were chosen and to clarify the equivalence of the retinol palmitate dose.

4. Page 5 Section 8.5

Change the concentration of Tween 80 in the vehicle from 0.4% to 0.2%.

Reason: Mistake in protocol.

# DRAFT

## PROTOCOL AMENDMENT

Study No.: 154  
Title: Developmental Toxicity (Segment II) Study of WR238605 Succinate in Rats

5. Page 8 Section

At the third paragraph, change postimplantation "death (s)" to postimplantation loss (es).

Reason: More accurate expression of the calculated parameter.

6. Page 9 Section 11

Delete "HRP, Inc." from the list of references.

Reason: Irrelevant reference.

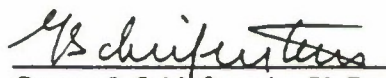
APPROVAL:

STUDY DIRECTOR:

  
Barry S. Levine, D.Sc., D.A.B.T.

10/28/94  
Date

SPONSOR APPROVAL:

  
George J. Schieferstein, Ph.D.  
Contracting Officer's  
Representative (COR)

10/24/94  
Date

DRAFT

APPENDIX 7  
Study Deviations

DRAFT

Contract No.: DAMD17-92-C-2001  
Task Order No.: UIC-10B  
Study No.: 154

DOSE RANGE-FINDING DEVELOPMENTAL  
TOXICITY STUDY OF WR238605 SUCCINATE IN RATS

Study Deviations\*

<u>Deviation Type</u>	<u>Specific Deviation</u>	<u>Effect on Study</u>
Protocol	Temperature was out of range on three occasions.	None; the deviations were minimal.
Protocol	A few litters (i.e., 3 - 4/dose) have disarticulated skeletons. Only 5 litters in the positive control dose group showed similar effects.	None; since the appearance of the disarticulated bones did not differ from those observed in the rest of the litters in each group.
Protocol	Relative uterine weight (% body weight) was not calculated.	None; mistake in protocol. Statistical analysis should be based on absolute uterine weights.

\*The detailed "Deviation Reports" are contained in the raw data which are archived at the Toxicology Research Laboratory, University of Illinois at Chicago, Department of Pharmacology, 1940 W. Taylor St., Chicago, Illinois, 60612.

The above deviations did not affect the integrity of the study.

\_\_\_\_\_  
Barry S. Levine, D.Sc., D.A.B.T.

\_\_\_\_\_  
Date